

SULFONAMIDE DERIVATIVES AS PPAR MODULATORS

FIELD OF THE INVENTION

5 The present invention relates to compounds of peroxisome proliferator activated receptor (PPAR) agonists, more specifically sulfonamide derivatives of PPAR agonists, which are useful for the treatment and/or prevention of disorders modulated by a PPAR agonist.

BACKGROUND OF THE INVENTION

10 The peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor gene family that are activated by fatty acids and fatty acid metabolites. The PPARs belong to the subset of nuclear receptors that function as
15 heterodimers with the 9-*cis* retinoic acid receptor (RXR). Three subtypes, designated PPAR α , PPAR γ and PPAR δ , are found in species ranging from *Xenopus* to humans.

 PPAR α is the main subtype in the liver and has facilitated analysis of the mechanism by which peroxisome proliferators exert their pleiotropic effects. PPAR α is activated by a number of medium and long-chain fatty acids, and it is involved in
20 stimulating β -oxidation of fatty acids. PPAR α is also involved with the activity of fibrates and fatty acids in rodents and humans. Fibrate acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma triglycerides along with moderate reduction in low-density lipoprotein (LDL) cholesterol, and they are used particularly for the treatment
25 of hypertriglyceridemia.

 PPAR γ is the main subtype in adipose tissue and involved in activating the program of adipocyte differentiation. PPAR γ is not involved in stimulating peroxisome proliferation in the liver. There are two isomers of PPAR γ : PPAR γ 1 and PPAR γ 2, which differ only in that PPAR γ 2 contains an additional 28 amino acids present at the amino
30 terminus. The DNA sequences for the PPAR γ receptors are described in Elbrecht, et al., BBRC 224:431-437 (1996). Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J₂ derivatives have been identified as natural ligands for PPAR γ , which also binds the anti-

diabetic agents thiazolidinediones with high affinity. The physiological functions of PPAR α and PPAR γ in lipid and carbohydrate metabolism were uncovered once it was recognized that they were the receptors for the fibrate and glitazone drugs, respectively.

PPAR α and PPAR γ receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, and gastrointestinal disease, such as inflammatory bowel disease and other inflammation related illnesses. Such inflammation related illnesses include, but are not limited to Alzheimer's disease, Crohn's disease, rheumatoid arthritis, psoriasis, and ischemia reprofusion injury.

By contrast, PPAR δ (also referred to as PPAR β and NUC1) is not reported to be receptor for any known class of drug molecules, and its role in mammalian physiology has remained undefined. The human nuclear receptor gene PPAR δ (hPPAR δ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, 6:1634-1641 (1992).

Diabetes is a disease in which a mammal's ability to regulate glucose levels in the blood is impaired because the mammal has a reduced ability to convert glucose to glycogen for storage in muscle and liver cells. In Type I diabetes, this reduced ability to store glucose is caused by reduced insulin production. "Type II Diabetes" or "non-insulin dependent diabetes mellitus" (NIDDM) is the form of diabetes, which is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. When these cells become desensitized to insulin, the body tries to compensate by producing abnormally high levels of insulin and hyperinsulemia results. Hyperinsulemia is associated with hypertension and elevated body weight. Since insulin is involved in promoting the cellular uptake of glucose, amino acids and triglycerides from the blood by insulin sensitive cells, insulin insensitivity can result in elevated levels of triglycerides and LDL (known as the "bad" cholesterol) which are risk factors in cardiovascular diseases. The constellation of symptoms which includes hyperinsulemia combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL is known as Syndrome X.

Hyperlipidemia is a condition which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The initial treatment for hypercholesterolemia is often a diet low in fat and cholesterol coupled with appropriate physical exercise. Drug intervention is initiated if LDL-lowering goals are not met by diet and exercise alone. It is desirable to lower elevated levels of LDL cholesterol and increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373- 381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL elevation are associated with undesirable effects, such as flushing.

There are several treatments currently available for treating diabetes mellitus but these treatments still remain unsatisfactory and have limitations. While physical exercise and reduction in dietary intake of calories will improve the diabetic condition, compliance with this approach can be poor because of sedentary lifestyles and excess food consumption, in particular high fat-containing food. Therefore, treatment with hypoglycemics, such as sulfonylureas (e.g., chlorpropamide, tolbutamide, tolazamide and acetohexamide) and biguanides (e.g. phenformin and metformin) are often necessary as the disease progresses. Sulfonylureas stimulate the β cells of the pancreas to secrete more insulin as the disease progresses. However, the response of the β cells eventually fails and treatment with insulin injections is necessary. In addition, both sulfonylurea treatment and insulin injection have the life threatening side effect of hypoglycemic coma, and thus patients using these treatments must carefully control dosage.

It has been well established that improved glycemic control in patients with diabetes (Type I and Type II) is accompanied by decreased microvascular complications (DCCT and UKPDS). Due to difficulty in maintaining adequate glycemic control over time in patients with Type II diabetes, the use of insulin sensitizers in the therapy of Type II diabetes is growing. There is also a growing body of evidence that

-4-

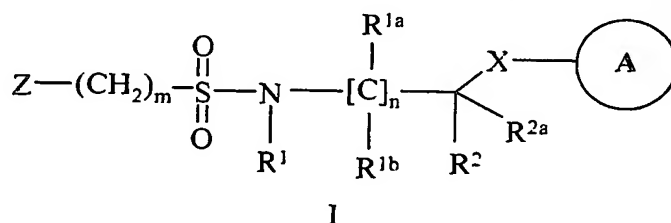
PPAR γ agonist, insulin sensitizer, may have benefits in the treatment of Type II diabetes beyond their effects in improving glycemic control.

In the last decade a class of compounds known as thiazolidinediones (e.g. U.S. Pat. Nos. 5,089,514; 4,342,771; 4,367,234; 4,340,605; and 5,306,726) have emerged as effective antidiabetic agents that have been shown to increase the sensitivity of insulin sensitive tissues, such as skeletal muscle, liver and adipose, to insulin. Increasing insulin sensitivity rather than the amount of insulin in the blood reduces the likelihood of hypoglycemic coma. Although thiazolidinediones have been shown to increase insulin sensitivity by binding to PPAR γ receptors, this treatment also produces unwanted side effects such as weight gain and, for troglitazone, liver toxicity.

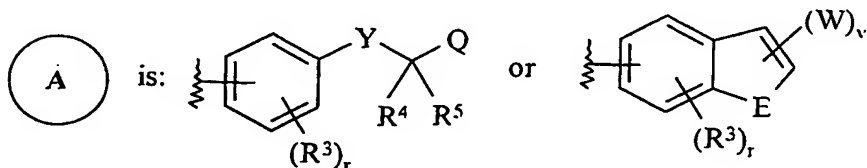
In view of the above, there exists a need for new pharmaceutical agents which modulate these receptors to prevent, treat and/or alleviate these diseases or conditions while ameliorating side effects of current treatments.

SUMMARY OF THE INVENTION

The present invention relates to a compound of novel peroxisome proliferator activated receptor (PPAR) agonist having a structural Formula I,

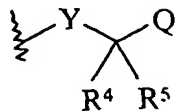


and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein:



E is: O, S or NR¹⁴;

-5-



W is: , hydrogen, C₁-C₆ alkyl, (CH₂)_n-C₃-C₆ cycloalkyl, haloalkyl or acyl;

Q is: -C(O)OR⁶ or R^{6A};

5 X is: a bond, C, O, S or S[O]_p;

Y is: a bond, S, C or O;

Z is: a) aliphatic group,

10 b) aryl,

c) a 5- to 10-membered heteroaryl wherein the heteroaryl containing at least one heteroatom selected from N, O or S,

d) bi-aryl, wherein biaryl being defined as aryl substituted with another aryl or aryl substituted with heteroaryl,

15 e) bi-heteroaryl, wherein bi-heteroaryl being defined as heteroaryl substituted with another heteroaryl, or heteroaryl substituted with aryl, and

f) heterocyclyl;

wherein aliphatic group, aryl, heteroaryl, bi-aryl, bi-heteroaryl and heterocyclyl being optionally substituted with one or more groups independently selected from R¹⁵;

20

m and n' are each independently: 0, 1, 2, 3 or 4;

n is: 0, 1, 2 or 3;

p is: 1 or 2;

25 r is: 1, 2, 3 or 4;

v is: 1 or 2;

R¹ is: hydrogen, wherein when Z is phenyl or naphthyl and R² is H, R¹ is not H, haloalkyl,

30 C₁-C₆ alkyl,

-6-

C₁-C₆ alkyl-C₁-C₆ alkoxy,
C₁-C₆ alkyl-aryl,
C₂-C₆ alkenyl,
C₂-C₆ alkynyl,
5 (CH₂)_n-C₃-C₆ cycloalkyl,
C₁-C₆ alkoxy,
aryl, or
R¹ and R² together being a 5- to 8-membered heterocyclyl ring, and
wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally
10 substituted with one or more groups independently selected from R¹⁵;

R^{1a} and R^{1b} are each independently:

hydrogen,
C₁-C₆ alkyl, or
15 R¹ and R^{1a}, R¹ and R^{1b}, R² and R^{1a}, R² and R^{1b} or R^{1a} and R^{1b} together being a 3- to
6-membered heterocyclyl or carbocyclyl ring where at least one of R^{1a} and R^{1b} is
not hydrogen;

R² is: hydrogen,
20 haloalkyl,
C₁-C₆ alkyl,
C₁-C₆ alkyl-C₁-C₆ alkoxy,
C₁-C₆ alkyl-aryl,
C₂-C₆ alkenyl,
25 C₂-C₆ alkynyl,
(CH₂)_n-C₃-C₆ cycloalkyl,
C₁-C₆ alkoxy,
aryl, or
R¹ and R² together being a 5- to 8-membered heterocyclyl ring, and
30 wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally
substituted with one or more groups independently selected from R¹⁵;

-7-

R^{2a} is: hydrogen, halo or C_1 - C_6 alkyl and wherein R^2 and R^{2a} together being a 3- to 8-membered ring; and wherein alkyl being optionally substituted with one or more groups independently selected from R^{15} ;

5 R^3 is: hydrogen,
halo,
cyano,
haloalkyl,
 C_1 - C_6 alkyl,
10 $(CH_2)_n$ - C_3 - C_6 cycloalkyl,
 $(C_1$ - C_4 alkyl)-heterocyclyl, wherein the heterocyclyl being optionally substituted with oxo,
 $(C_1$ - C_4 alkyl)- $NR^7C(O)_pR^9$, and
wherein alkyl, cycloalkyl and heterocyclyl being optionally substituted with one
15 or more groups independently selected from R^{15} ;

R^4 and R^5 are each independently:

hydrogen,
halo,
20 C_1 - C_6 alkyl
 C_1 - C_6 alkoxy;
aryloxy;
 $N(R^8)_2$,
 SR^8 or
25 R^4 and R^5 together being a 3- to 8-membered ring;

R^6 is: hydrogen, C_1 - C_6 alkyl or aminoalkyl;

R^{6A} is: carboxamide, C_1 - C_3 alkylnitrile, sulfonamide, acylsulfonamide or tetrazole;

R^7 is: hydrogen or C_1 - C_6 alkyl;

-8-

R⁸ and R⁹ are each independently:

hydrogen, C₁-C₆ alkyl, aryl, heteroaryl, or heterocyclyl, and
wherein aryl, heteroaryl and heterocyclyl being optionally substituted with one or
more substituents selected from the group consisting of hydrogen, nitro, cyano,
5 hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C₁-C₆ alkyl and C₁-C₆
alkoxy;

R¹⁴ is: hydrogen, aryl, C₁-C₆ alkyl, or C₁-C₆ alkyl-COOR⁶, and
wherein aryl and alkyl being optionally substituted with one or more groups
10 independently selected from R¹⁵; and

R¹⁵ is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C₁-
C₆ alkyl, C₁-C₆ alkoxy, N(R⁸)₂, NR⁸S(O)₂R⁹, NR⁸C(O)_pR⁹, C(O)NR⁸R⁹, C(O)_pR⁸,
SR⁸, S(O)_pR⁸ or S(O)₂NR⁸R⁹.

15 The compounds of the present invention are useful in the treatment or
prevention of diseases or condition relates to hyperglycemia, dyslipidemia, Type II
diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart
failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity,
anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where
20 insulin resistance is a component.

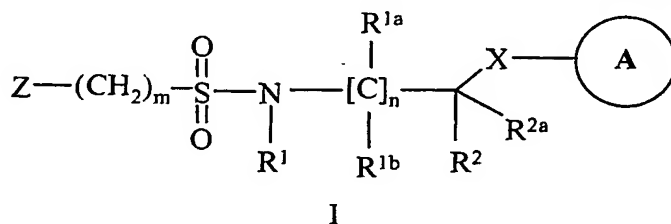
In one embodiment, the present invention also relates to pharmaceutical
compositions which comprising at least one compound of the present invention, or a
pharmaceutically acceptable salt, solvate, hydrate thereof and a pharmaceutically
acceptable carrier. Within the scope of this invention also include a pharmaceutical
25 composition containing additional therapeutic agent as well as at least one compound of
the present invention, or a pharmaceutically acceptable salt, solvate, hydrate thereof and a
pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of
modulating a PPAR by contacting the receptor with at least one compound of the present
30 invention, and pharmaceutically acceptable salts, solvates and hydrates thereof.

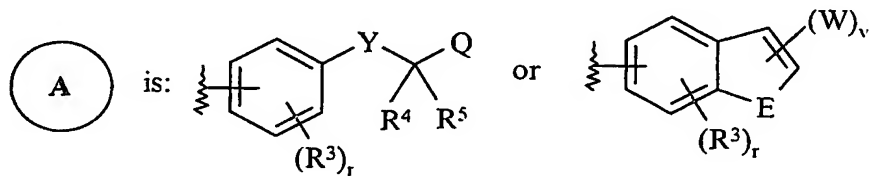
DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are directed to peroxisome proliferator activated receptor (PPAR) agonists, more specifically sulfonamide derivatives of PPAR agonists. The compounds of the present invention are also relates to PPAR γ/δ dual agonists, which are useful for the treatment and/or prevention of disorders modulated by a PPAR.

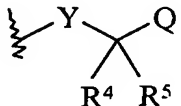
An embodiment of the present invention is a compound of novel peroxisome proliferator activated receptor (PPAR) agonists having a structural Formula I,



and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein:



E is: O, S or NR^{14} ;

W is: , hydrogen, C_1 - C_6 alkyl, $(\text{CH}_2)_n$ - C_3 - C_6 cycloalkyl, haloalkyl or acyl;
Q is: $-\text{C}(\text{O})\text{OR}^6$ or R^{6A} ;

X is: a bond, C, O, S or $\text{S}[\text{O}]_p$;

Y is: a bond, S, C or O;

Z is: a) aliphatic group,

-10-

- b) aryl,
- c) a 5- to 10-membered heteroaryl wherein the heteroaryl containing at least one heteroatom selected from N, O or S,
- d) bi-aryl, wherein biaryl being defined as aryl substituted with another aryl or aryl substituted with heteroaryl,
- e) bi-heteroaryl, wherein bi-heteroaryl being defined as heteroaryl substituted with another heteroaryl, or heteroaryl substituted with aryl, and
- f) heterocyclyl;

wherein aliphatic group, aryl, heteroaryl, bi-aryl, bi-heteroaryl and heterocyclyl being optionally substituted with one or more groups independently selected from R^{15} ;

m and n' are each independently: 0, 1, 2, 3 or 4;

n is: 0, 1, 2 or 3;

p is: 1 or 2;

r is: 1, 2, 3 or 4;

v is: 1 or 2;

R^1 is: hydrogen, wherein when Z is phenyl or naphthyl and R^2 is H, R^1 is not H, haloalkyl,

C_1 - C_6 alkyl,

C_1 - C_6 alkyl- C_1 - C_6 alkoxy,

C_1 - C_6 alkyl-aryl,

C_2 - C_6 alkenyl,

C_2 - C_6 alkynyl,

$(CH_2)_n$ - C_3 - C_6 cycloalkyl,

C_1 - C_6 alkoxy,

aryl, or

R^1 and R^2 together being a 5- to 8-membered heterocyclyl ring, and

wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally substituted with one or more groups independently selected from R^{15} ;

-11-

R^{1a} and R^{1b} are each independently:

hydrogen,

C_1 - C_6 alkyl, or

5 R^1 and R^{1a} , R^1 and R^{1b} , R^2 and R^{1a} , R^2 and R^{1b} or R^{1a} and R^{1b} together being a 3- to 6-membered heterocyclyl or carbocyclyl ring where at least one of R^{1a} and R^{1b} is not hydrogen;

R^2 is: hydrogen,

haloalkyl,

10 C_1 - C_6 alkyl,

C_1 - C_6 alkyl- C_1 - C_6 alkoxy,

C_1 - C_6 alkyl-aryl,

C_2 - C_6 alkenyl,

C_2 - C_6 alkynyl,

15 $(CH_2)_n$ - C_3 - C_6 cycloalkyl,

C_1 - C_6 alkoxy,

aryl, or

R^1 and R^2 together being a 5- to 8-membered heterocyclyl ring, and

20 wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally substituted with one or more groups independently selected from R^{15} ;

R^{2a} is: hydrogen, halo or C_1 - C_6 alkyl and wherein R^2 and R^{2a} together being a 3- to 8-membered ring; and wherein alkyl being optionally substituted with one or more groups independently selected from R^{15} ;

25

R^3 is: hydrogen,

halo,

cyano,

haloalkyl,

30 C_1 - C_6 alkyl,

$(CH_2)_n$ - C_3 - C_6 cycloalkyl,

-12-

(C₁-C₄ alkyl)-heterocyclyl, wherein the heterocyclyl being optionally substituted with oxo,

(C₁-C₄ alkyl)-NR⁷C(O)_pR⁹, and

wherein alkyl, cycloalkyl and heterocyclyl being optionally substituted with one or more groups independently selected from R¹⁵;

R⁴ and R⁵ are each independently:

hydrogen,

halo,

C₁-C₆ alkyl

C₁-C₆ alkoxy;

aryloxy;

N(R⁸)₂,

SR⁸ or

R⁴ and R⁵ together being a 3- to 8-membered ring;

R⁶ is: hydrogen, C₁-C₆ alkyl or aminoalkyl;

R^{6A} is: carboxamide, C₁-C₃ alkyl nitrile, sulfonamide, acylsulfonamide or tetrazole;

R⁷ is: hydrogen or C₁-C₆ alkyl;

R⁸ and R⁹ are each independently:

hydrogen, C₁-C₆ alkyl, aryl, heteroaryl, or heterocyclyl, and

wherein aryl, heteroaryl and heterocyclyl being optionally substituted with one or more substituents selected from the group consisting of hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C₁-C₆ alkyl and C₁-C₆ alkoxy;

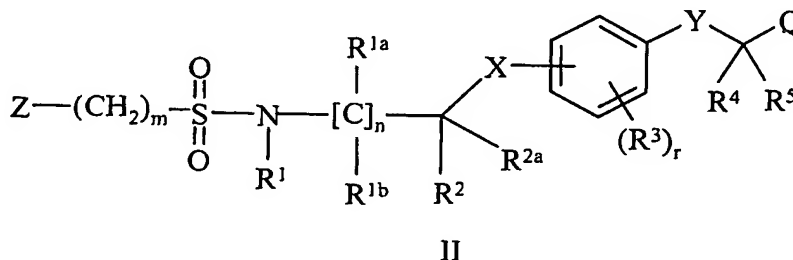
R¹⁴ is: hydrogen, aryl, C₁-C₆ alkyl, or C₁-C₆ alkyl-COOR⁶, and

wherein aryl and alkyl being optionally substituted with one or more groups independently selected from R¹⁵; and

-13-

R^{15} is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $(CH_2)_n$ - C_3 - C_6 cycloalkyl, $N(R^8)_2$, $NR^8S(O)_2R^9$, $NR^8C(O)_pR^9$, $C(O)NR^8R^9$, $C(O)_pR^8$, SR^8 , $S(O)_pR^8$ or $S(O)_2NR^8R^9$.

A preferred embodiment of the present invention is a compound having a structural Formula II,



and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein:

Q is: $-C(O)OR^6$ or R^{6A} ;

X is: a bond, C, O, S or $S[O]_p$;

Y is: a bond, S, C or O;

Z is: a) aliphatic group,

b) aryl,

c) a 5- to 10-membered heteroaryl wherein the heteroaryl containing at least one heteroatom selected from N, O or S,

d) bi-aryl, wherein biaryl being defined as aryl substituted with another aryl or aryl substituted with heteroaryl,

e) bi-heteroaryl, wherein bi-heteroaryl being defined as heteroaryl substituted with another heteroaryl, or heteroaryl substituted with aryl, and

f) heterocyclyl;

wherein aliphatic group, aryl, heteroaryl, bi-aryl, bi-heteroaryl and heterocyclyl being optionally substituted with one or more groups independently selected from R^{15} ;

m and n' are each independently: 0, 1, 2, 3 or 4;

-14-

n is: 0, 1, 2 or 3;

p is: 1 or 2;

r is: 1, 2, 3 or 4;

5 R¹ is: aryl

haloalkyl,

C₁-C₆ alkyl,C₁-C₆ alkyl-C₁-C₆ alkoxy,C₁-C₆ alkyl-aryl,10 C₂-C₆ alkenyl,C₂-C₆ alkynyl,(CH₂)_n-C₃-C₆ cycloalkyl,C₁-C₆ alkoxy orR¹ and R² together being a 5- to 8-membered heterocyclyl ring, and15 wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally substituted with one or more groups independently selected from R¹⁵;R^{1a} and R^{1b} are each independently:

hydrogen,

20 C₁-C₆ alkyl, orR¹ and R^{1a}, R¹ and R^{1b}, R² and R^{1a}, R² and R^{1b} or R^{1a} and R^{1b} together being a 3- to 6-membered heterocyclyl or carbocyclyl ring where at least one of R^{1a} and R^{1b} is not hydrogen;25 R² is: hydrogen,

haloalkyl,

C₁-C₆ alkyl,C₁-C₆ alkyl-C₁-C₆ alkoxy,C₁-C₆ alkyl-aryl,30 C₂-C₆ alkenyl,C₂-C₆ alkynyl,(CH₂)_n-C₃-C₆ cycloalkyl,

-15-

C₁-C₆ alkoxy,

aryl, or

R¹ and R² together being a 5- to 8-membered heterocyclyl ring, and

5 wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally substituted with one or more groups independently selected from R¹⁵;

R^{2a} is: hydrogen, halo or C₁-C₆ alkyl and wherein R² and R^{2a} together being a 3- to 8-membered ring; and wherein alkyl being optionally substituted with one or more groups independently selected from R¹⁵;

10

R³ is: hydrogen,

halo,

cyano,

haloalkyl,

15

C₁-C₆ alkyl,

(CH₂)_n-C₃-C₆ cycloalkyl,

(C₁-C₄ alkyl)-heterocyclyl, wherein the heterocyclyl being optionally substituted with oxo,

(C₁-C₄ alkyl)-NR⁷C(O)_pR⁹, and

20

wherein alkyl, cycloalkyl and heterocyclyl being optionally substituted with one or more groups independently selected from R¹⁵;

R⁴ and R⁵ are each independently:

hydrogen,

25

halo,

C₁-C₆ alkyl

C₁-C₆ alkoxy;

aryloxy;

N(R⁸)₂,

30

SR⁸ or

R⁴ and R⁵ together being a 3- to 8-membered ring;

-16-

R^6 is: hydrogen, C_1 - C_6 alkyl or aminoalkyl;

R^{6A} is: carboxamide, C_1 - C_3 alkyl nitrile, sulfonamide, acylsulfonamide or tetrazole;

5 R^7 is: hydrogen or C_1 - C_6 alkyl;

R^8 and R^9 are each independently:

hydrogen, C_1 - C_6 alkyl, aryl, heteroaryl, or heterocyclyl, and
 wherein aryl, heteroaryl and heterocyclyl being optionally substituted with one or
 10 more substituents selected from the group consisting of hydrogen, nitro, cyano,
 hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C_1 - C_6 alkyl and C_1 - C_6
 alkoxy;

15 R^{15} is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C_1 -
 C_6 alkyl, C_1 - C_6 alkoxy, $(CH_2)_n$ - C_3 - C_6 cycloalkyl, $N(R^8)_2$, $NR^8S(O)_2R^9$,
 $NR^8C(O)_pR^9$, $C(O)NR^8R^9$, $C(O)_pR^8$, SR^8 , $S(O)_pR^8$ or $S(O)_2NR^8R^9$.

The compound as recited above, wherein X and Y are respectively S and
 O; S and C; or C and O.

20 The compounds of Formula I and II as recited above, wherein Z is C_1 - C_6
 alkyl, aryl or heteroaryl.

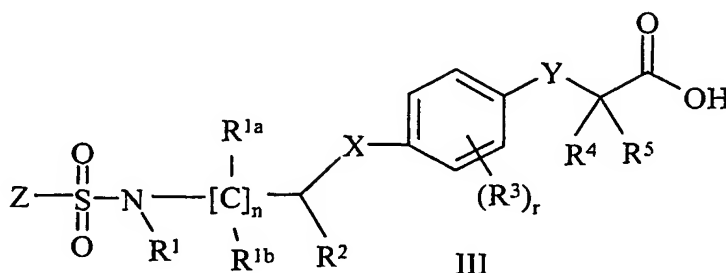
The compounds of Formula I and II as recited above, wherein Z is phenyl,
 naphthyl, thiophenyl, oxazolyl, isooxazolyl, pyridyl, benzothiophenyl, benzofuranyl,
 indolyl, isoindolyl, pyrazolyl, imidazolyl, 1,4 benzodioxan, benzooxazolyl,
 benzothiazolyl, benzoimidazolyl, or 2,3-dihydrobenzofuranyl.

25 The compounds of Formula I and II as recited above, wherein R^1 is C_3 - C_6
 alkyl or $(CH_2)_n$ - C_3 - C_6 cycloalkyl; R^2 and R^3 are each independently C_1 - C_3 alkyl; and r is
 1.

The compounds of Formula I and II as recited above, wherein X is
 positioned para to Y; and R^3 is positioned ortho to Y.

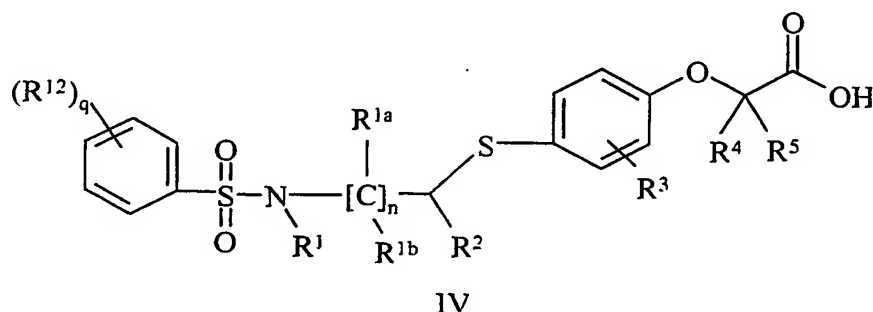
-17-

Another preferred embodiment of the present invention is a compound having a structural Formula III,



- 5 and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein,
- n is: 1 or 2;
- r is: 1, 2, 3, or 4;
- X is: S or C;
- 10 Y is: C or O;
- Z is: aryl or a 5- to 10-membered heteroaryl,
- wherein aryl and heteroaryl being optionally substituted with one or more groups independently selected from R^{15} ;
- R^1 and R^2 are each independently: C_1 - C_6 alkyl or $(CH_2)_n$ - C_3 - C_6 cycloalkyl; and
- 15 R^{1a} and R^{1b} , R^3 , R^4 and R^5 are each independently: hydrogen or C_1 - C_6 alkyl.

Yet another preferred embodiment of the present invention is the compound having a structural Formula IV,



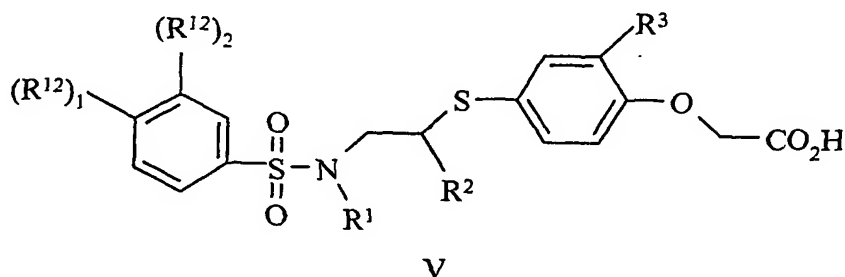
- and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof,
- 20 wherein:
- q is 1, 2, 3, 4, or 5;
- R^8 and R^9 are each independently:
- hydrogen, C_1 - C_6 alkyl, aryl, heteroaryl, or heterocyclyl,

-18-

wherein alkyl, aryl, heteroaryl and heterocyclyl being optionally substituted with one or more substituents selected from the group consisting of hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C₁-C₆ alkyl and C₁-C₆ alkoxy; and

- 5 R¹² is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryl, heteroaryl, aryloxy, oxo, C₁-C₆ alkyl, C₁-C₆ alkoxy, (CH₂)_n-C₃-C₆ cycloalkyl, N(R⁸)₂, NR⁸S(O)₂R⁹, NR⁸C(O)_pR⁹, C(O)NR⁸R⁹, C(O)_pR⁸, SR⁸, S(O)_pR⁸ or S(O)₂NR⁸R⁹.

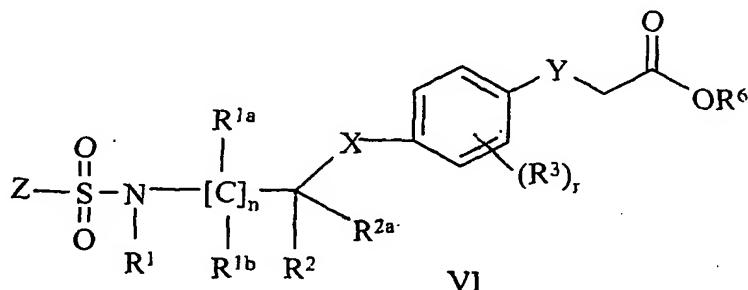
Yet another preferred embodiment of the present invention is the compound having a structural Formula V,



10 and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein: R¹ and R² are each independently C₁-C₄ alkyl or (CH₂)_n-C₃-C₆ cycloalkyl; R³ is C₁-C₄ alkyl; (R¹²)₁ is halo, haloalkyl, or haloalkyloxy; and (R¹²)₂ is F, Cl or Br.

- The compound as recited above, wherein R¹ is methyl, ethyl, propyl, cyclopropyl, cyclopropylmethyl, cyclobutyl; R³ is methyl and (R¹²)₁ is OCF₃.

Yet another embodiment of the present invention is a compound having a structural Formula VI,



and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof,

- 20 wherein:

X is: a bond, C, O, S or S[O]_p;

-19-

Y is: a bond, S, C or O;

Z is: heteroaryl wherein the heteroaryl containing at least one heteroatom selected from N, O or S, and wherein heteroaryl being optionally substituted with one or more groups selected from R¹⁵;

n is: 0, 1, 2 or 3;

n' is: 0, 1, 2, 3 or 4;

p is: 1 or 2;

r is: 1, 2, 3 or 4;

R¹ is: hydrogen,

haloalkyl,

C₁-C₆ alkyl,

C₁-C₆ alkyl-C₁-C₆ alkoxy,

C₁-C₆ alkyl-aryl,

C₂-C₆ alkenyl,

C₂-C₆ alkynyl,

(CH₂)_n-C₃-C₆ cycloalkyl,

C₁-C₆ alkoxy,

aryl, or

R¹ and R² together being a 5- to 8-membered heterocyclyl ring, and

wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally substituted with one or more groups independently selected from R¹⁵;

R^{1a} and R^{1b} are each independently:

hydrogen,

C₁-C₆ alkyl, or

R¹ and R^{1a}, R¹ and R^{1b}, R² and R^{1a}, R² and R^{1b} or R^{1a} and R^{1b} together being a 3- to 6-membered heterocyclyl or carbocyclyl ring where at least one of R^{1a} and R^{1b} is not hydrogen;

-20-

R² is: hydrogen,

haloalkyl,

C₁-C₆ alkyl,

C₁-C₆ alkyl-C₁-C₆ alkoxy,

5 C₁-C₆ alkyl-aryl,

C₂-C₆ alkenyl,

C₂-C₆ alkynyl,

(CH₂)_n-C₃-C₆ cycloalkyl,

C₁-C₆ alkoxy,

10 aryl, or

R¹ and R² together being a 5- to 8-membered heterocyclyl ring, and

wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally substituted with one or more groups independently selected from R¹⁵;

15 R^{2a} is: hydrogen, halo or C₁-C₆ alkyl and wherein R² and R^{2a} together being a 3- to 8-membered ring; and wherein alkyl being optionally substituted with one or more groups independently selected from R¹⁵;

R³ is: hydrogen,

20 halo,

cyano,

haloalkyl,

C₁-C₆ alkyl,

(CH₂)_n-C₃-C₆ cycloalkyl,

25 (C₁-C₄ alkyl)-heterocyclyl, wherein the heterocyclyl being optionally substituted with oxo,

(C₁-C₄ alkyl)-NR⁷C(O)_pR⁹, and

wherein alkyl, cycloalkyl and heterocyclyl being optionally substituted with one or more groups independently selected from R¹⁵;

30

-21-

R^6 is: hydrogen, C_1 - C_6 alkyl or aminoalkyl;

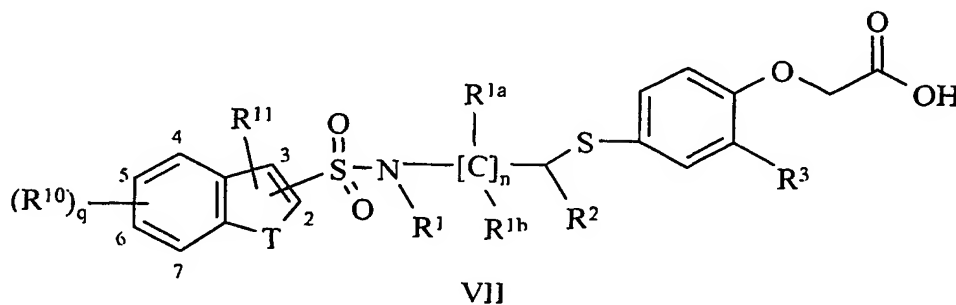
R^7 is: hydrogen or C_1 - C_6 alkyl;

5 R^8 and R^9 are each independently:

hydrogen, C_1 - C_6 alkyl, aryl, heteroaryl, or heterocyclyl, and
 wherein aryl, heteroaryl and heterocyclyl being optionally substituted with one or
 more substituents selected from the group consisting of hydrogen, nitro, cyano,
 hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C_1 - C_6 alkyl and C_1 - C_6
 10 alkoxy; and

R^{15} is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C_1 -
 C_6 alkyl, C_1 - C_6 alkoxy, $(CH_2)_n$ - C_3 - C_6 cycloalkyl, $N(R^8)_2$, $NR^8S(O)_2R^9$,
 $NR^8C(O)_pR^9$, $C(O)NR^8R^9$, $C(O)_pR^8$, SR^8 , $S(O)_pR^8$ or $S(O)_2NR^8R^9$.

15 Yet another preferred embodiment of the present invention is the
 compound having a structural Formula VII,



and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof,

20 wherein:

q is: 1, 2, 3, or 4;

T is: O , NR^{1c} or S ;

R^{1c} is: hydrogen or C_1 - C_6 alkyl;

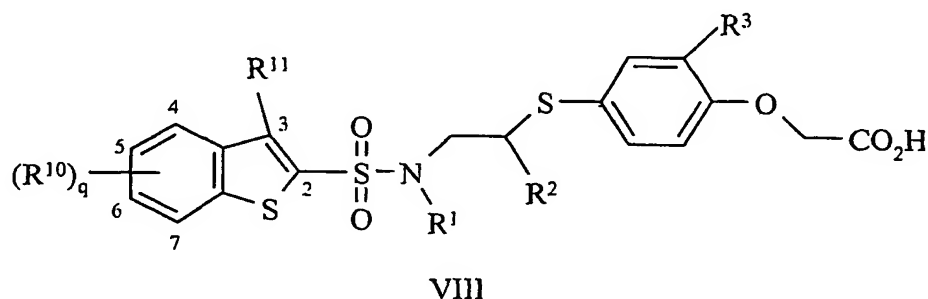
25 R^{10} and R^{11} are each independently:

hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy,
 C_1 - C_6 alkyl or C_1 - C_6 alkoxy; and

-22-

wherein alkyl, aryloxy, and alkoxy being optionally substituted with one or more groups independently selected from R^{15} .

Yet another preferred embodiment of the present invention is the compound having a structural Formula VIII,



5

wherein:

q is: 1 or 2;

R^1 is: C_3 - C_5 alkyl or $(CH_2)_n$ - C_3 - C_6 cycloalkyl;

R^2 and R^3 are each independently: C_1 - C_3 alkyl;

10 R^{10} is: halo, haloalkyl or C_1 - C_3 alkyl, and

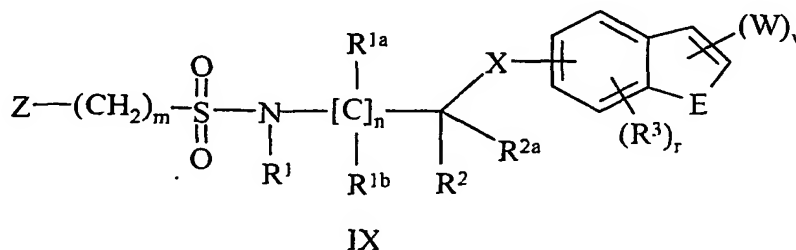
wherein R^{10} being substituted at a position 5, or 6, or both 5 and 6 of benzothiophenyl ring; and

R^{11} is: hydrogen or C_1 - C_6 alkyl.

The compound as recited above, wherein R^{10} is Cl, F, Br, CH_3 or CF_3

15 being substituted at a position 5 of benzothiophenyl ring.

Yet another preferred embodiment of the present invention is a compound having a structural Formula IX,

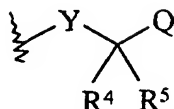


and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof,

20 wherein:

E is: O, S or NR^{14} ;

-23-



W is: R^4 , R^5 , hydrogen, C_1 - C_6 alkyl, $(CH_2)_n$ - C_3 - C_6 cycloalkyl, haloalkyl or acyl;

Q is: $-C(O)OR^6$ or R^{6A} ;

5 X is: a bond, C, O, S or $S[O]_p$;

Y is: a bond, S, C or O;

- 10 Z is:
- a) aliphatic group,
 - b) aryl,
 - c) a 5- to 10-membered heteroaryl wherein the heteroaryl containing at least one heteroatom selected from N, O or S,
 - d) bi-aryl, wherein biaryl being defined as aryl substituted with another aryl or aryl substituted with heteroaryl,
 - 15 e) bi-heteroaryl, wherein bi-heteroaryl being defined as heteroaryl substituted with another heteroaryl, or heteroaryl substituted with aryl, and
 - f) heterocyclyl;
- wherein aliphatic group, aryl, heteroaryl, bi-aryl, bi-heteroaryl and heterocyclyl being optionally substituted with one or more groups independently selected from R^{15} ;
- 20

m and n are each independently: 0, 1, 2, 3 or 4;

n is: 0, 1, 2 or 3;

p is: 1 or 2;

25 r is: 1, 2, 3 or 4;

v is: 1 or 2;

R^1 is: hydrogen,
haloalkyl,
30 C_1 - C_6 alkyl,

-24-

C₁-C₆ alkyl-C₁-C₆ alkoxy,

C₁-C₆ alkyl-aryl,

C₂-C₆ alkenyl,

C₂-C₆ alkynyl,

5 (CH₂)_n-C₃-C₆ cycloalkyl,

C₁-C₆ alkoxy,

aryl, or

R¹ and R² together being a 5- to 8-membered heterocyclyl ring, and

wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally

10 substituted with one or more groups independently selected from R¹⁵;

R^{1a} and R^{1b} are each independently:

hydrogen,

C₁-C₆ alkyl, or

15 R¹ and R^{1a}, R¹ and R^{1b}, R² and R^{1a}, R² and R^{1b} or R^{1a} and R^{1b} together being a 3- to 6-membered heterocyclyl or carbocyclyl ring where at least one of R^{1a} and R^{1b} is not hydrogen;

R² is: hydrogen,

20 haloalkyl,

C₁-C₆ alkyl,

C₁-C₆ alkyl-C₁-C₆ alkoxy,

C₁-C₆ alkyl-aryl,

C₂-C₆ alkenyl,

25 C₂-C₆ alkynyl,

(CH₂)_n-C₃-C₆ cycloalkyl,

C₁-C₆ alkoxy,

aryl, or

R¹ and R² together being a 5- to 8-membered heterocyclyl ring, and

30 wherein alkyl, aryl, alkenyl, alkynyl, cycloalkyl and alkoxy being optionally substituted with one or more groups independently selected from R¹⁵;

-25-

R^{2a} is: hydrogen, halo or C_1 - C_6 alkyl and wherein R^2 and R^{2a} together being a 3- to 8-membered ring; and wherein alkyl being optionally substituted with one or more groups independently selected from R^{15} ;

5 R^3 is: hydrogen,
halo,
cyano,
haloalkyl,
 C_1 - C_6 alkyl,
10 $(CH_2)_n$ - C_3 - C_6 cycloalkyl,
 $(C_1$ - C_4 alkyl)-heterocyclyl, wherein the heterocyclyl being optionally substituted
with oxo,
 $(C_1$ - C_4 alkyl)- $NR^7C(O)_pR^9$, and
wherein alkyl, cycloalkyl and heterocyclyl being optionally substituted with one
15 or more groups independently selected from R^{15} ;

R^4 and R^5 are each independently:

hydrogen,
halo,
20 C_1 - C_6 alkyl
 C_1 - C_6 alkoxy;
aryloxy;
 $N(R^8)_2$.
 SR^8 or
25 R^4 and R^5 together being a 3- to 8-membered ring;

R^6 is: hydrogen, C_1 - C_6 alkyl or aminoalkyl;

R^{6A} is: carboxamide, C_1 - C_3 alkyl nitrile, sulfonamide, acylsulfonamide or tetrazole;

30 R^7 is: hydrogen or C_1 - C_6 alkyl;

-26-

R^8 and R^9 are each independently:

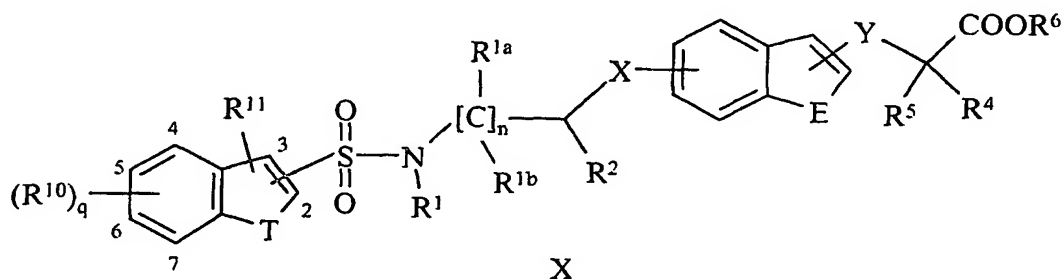
hydrogen, C_1 - C_6 alkyl, aryl, heteroaryl, or heterocyclyl, and
 wherein aryl, heteroaryl and heterocyclyl being optionally substituted with one or
 more substituents selected from the group consisting of hydrogen, nitro, cyano,
 5 hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C_1 - C_6 alkyl and C_1 - C_6
 alkoxy;

R^{14} is: hydrogen, aryl, C_1 - C_6 alkyl, or C_1 - C_6 alkyl-COOR⁶, and

wherein aryl and alkyl being optionally substituted with one or more groups
 10 independently selected from R^{15} ; and

R^{15} is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, C_1 -
 C_6 alkyl, C_1 - C_6 alkoxy, $(CH_2)_n$ - C_3 - C_6 cycloalkyl, $N(R^8)_2$, $NR^8S(O)_2R^9$,
 $NR^8C(O)_pR^9$, $C(O)NR^8R^9$, $C(O)_pR^8$, SR^8 , $S(O)_pR^8$ or $S(O)_2NR^8R^9$.

15 Yet another preferred embodiment of the present invention is the
 compound having a structural Formula X,



and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof,
 wherein:

20 n and q are each independently: 1, 2, 3 or 4;

T is: O, NR^{1c} or S;

X is: C, O or S;

R^1 is: hydrogen, C_1 - C_6 alkyl or $(CH_2)_n$ - C_3 - C_6 cycloalkyl;

R^{1a} , R^{1b} , R^{1c} and R^2 are each independently: hydrogen or C_1 - C_6 alkyl; and

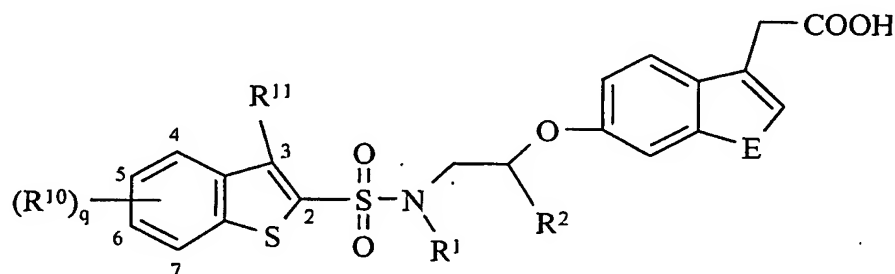
25 R^{10} and R^{11} are each independently:

hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy,

-27-

C₁-C₆ alkyl or C₁-C₆ alkoxy; and wherein alkyl, alkoxy and aryloxy being optionally substituted with one or more groups selected from R¹⁵.

Yet another preferred embodiment of the present invention is the compound having a structural Formula XI,



XI

and pharmaceutically acceptable salts, solvates, hydrates or stereoisomers thereof, wherein:

q is 1 or 2;

E is O, S or NR¹⁴;

10 R¹, R² and R¹¹ are each independently: C₁-C₄ alkyl;

R¹⁰ is: Cl, F, Br, CH₃ or CF₃, and wherein R¹⁰ being substituted at a position 5, or 6, or both 5 and 6 of benzothiophenyl ring; and

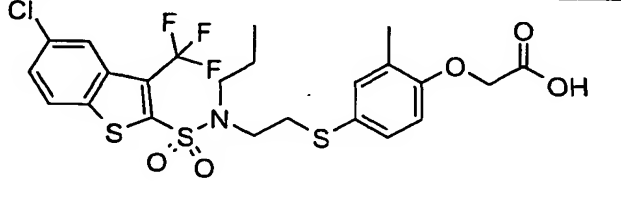
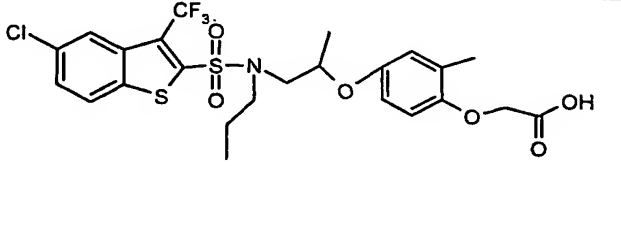
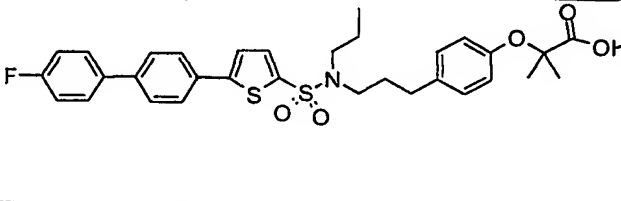
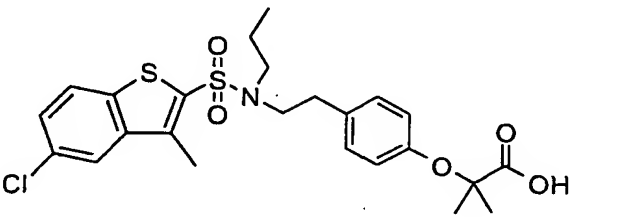
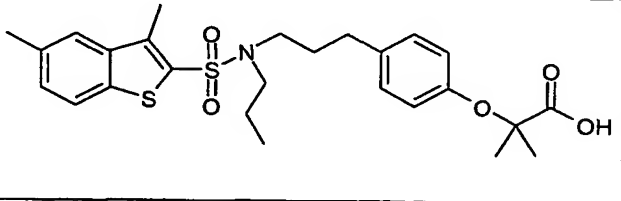
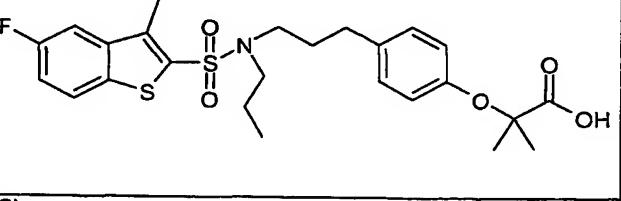
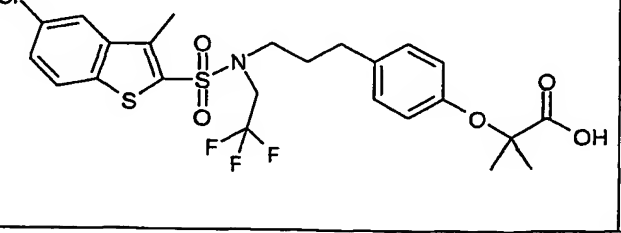
R¹⁴ is: hydrogen, C₁-C₆ alkyl or aryl.

The most preferred embodiment of the present invention is the compounds

15 listed below:

No.	Structure	Name
1		3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenyl)-propionic acid
2		3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenyl)-propionic acid

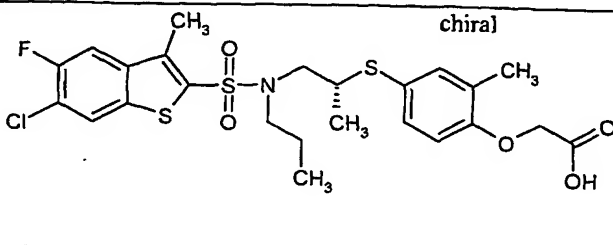
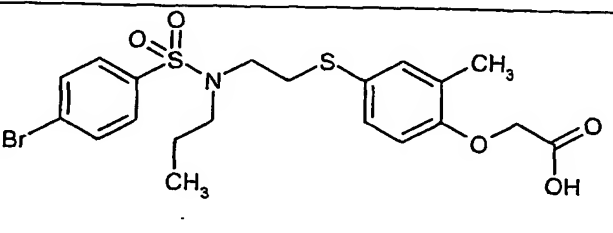
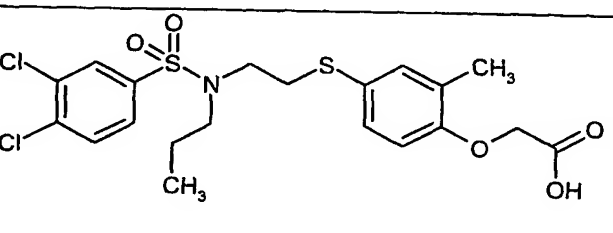
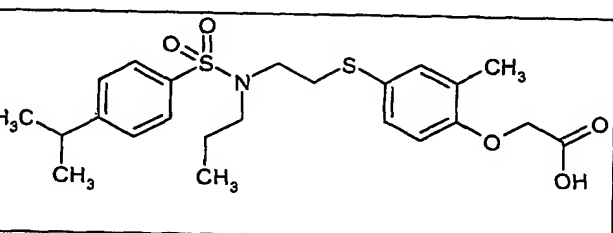
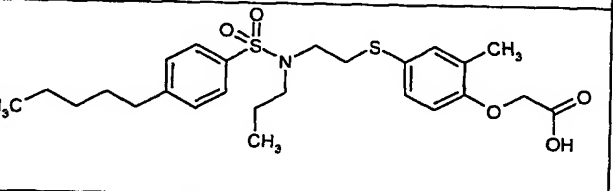
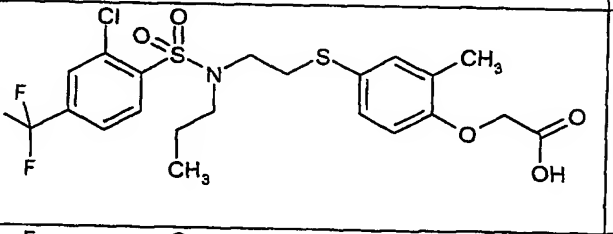
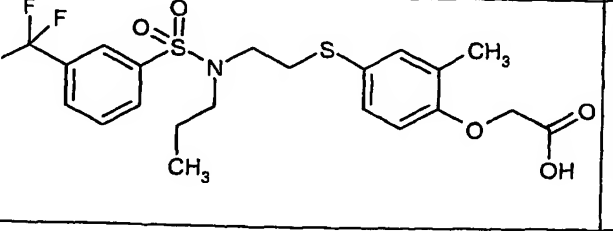
No.	Structure	Name
3		(4-{2-[(5-Chloro-3-methyl-benzofuran-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid
4		(4-{2-[(5-Chloro-3-methyl-benzofuran-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
5		3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenyl)-propionic acid
6		(4-{2-[(5-Chloro-3-ethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
7		4-{2-[(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
8		4-{2-[(7-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
9		(4-{2-[(4-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

No.	Structure	Name
10		(4-{2-[(5-Chloro-3-trifluoromethyl)-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
11		(4-{2-[(5-Chloro-3-trifluoromethyl)-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid
12		2-[4-(3-{[5-(4'-Fluoro-biphenyl-4-yl)-thiophene-2-sulfonyl]-propyl-amino}-propyl)-phenoxy]-2-methyl-propionic acid
13		2-(4-{2-[(5-Chloro-3-methyl)-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl}-phenoxy)-2-methyl-propionic acid
14		2-(4-{3-[(3,5-Dimethyl)-benzo[b]thiophene-2-sulfonyl]-propyl-amino}-propyl)-phenoxy)-2-methyl-propionic acid
15		2-(4-{3-[(5-Fluoro-3-methyl)-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid
16		2-(4-{3-[(5-Chloro-3-methyl)-benzo[b]thiophene-2-sulfonyl)-(2,2,2-trifluoroethyl)-amino]-propyl}-phenoxy)-2-methyl-propionic acid

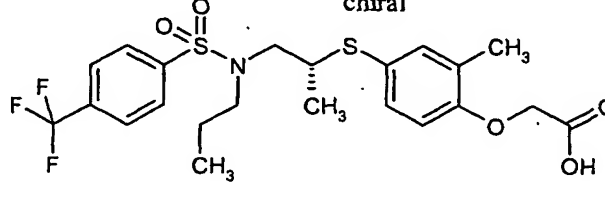
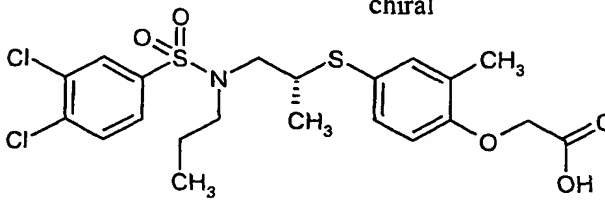
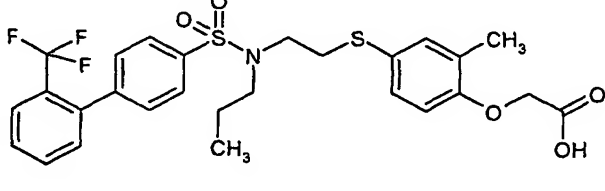
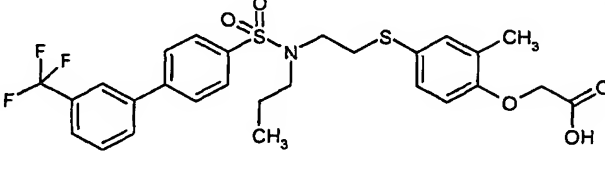
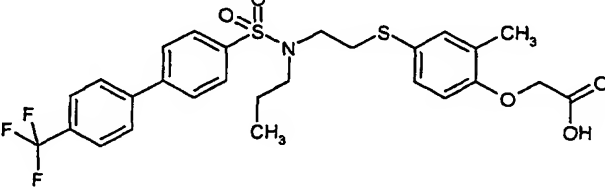
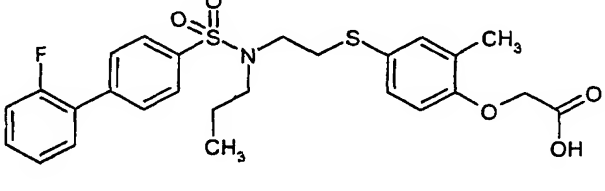
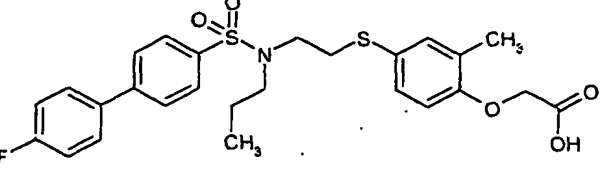
No.	Structure	Name
17		2-(4-{2-[(3-Ethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-3-propyl-phenoxy)-2-methyl-propionic acid
18		2-[4-(1-{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-2-methyl-phenoxy]-2-methyl-propionic acid
19		3-[4-(1-{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-2-methyl-phenyl]-propionic acid
20		[4-(1-{[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid
21		[4-(1-{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid
22		[4-(1-{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid

No.	Structure	Name
23		(2-Methyl-4-{2-[(6-phenoxy-pyridine-3-sulfonyl)-propyl-amino]-ethylsulfanyl} phenoxy)-acetic acid
24		(2-Methyl-4-{2-[(5-methyl-1-phenyl-1H-pyrazole-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
25		(2-Methyl-4-{2-[(4-oxazol-5-yl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
26		(2-Methyl-4-{2-[propyl-(4-pyrazol-1-yl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
27		(2-Methyl-4-{2-[(2-naphthalen-1-yl-ethanesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
28		(2-Methyl-4-{2-[propyl-(4-trifluoromethylphenylmethanesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
29		(4-{2-[(Biphenyl-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid

No.	Structure	Name
30		(4-{2-[(2,3-Dihydrobenzo[1,4]dioxine-6-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid
31		[2-Methyl-4-(2-{[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-propyl-amino}-ethylsulfanyl)-phenoxy]-acetic acid
32		[2-Methyl-4-(2-{[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-propyl-amino}-ethylsulfanyl)-phenoxy]-acetic acid
33		[2-Methyl-4-(2-{[5-(1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-propyl-amino}-ethylsulfanyl)-phenoxy]-acetic acid
34		(R)-(2-Methyl-4-{1-methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
35		(R)-3-(4-{2-[(6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenyl)-propionic acid

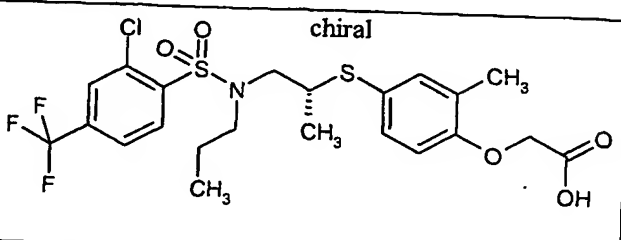
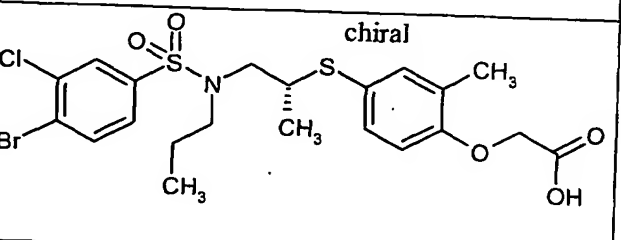
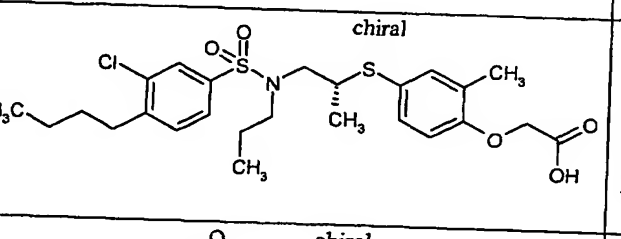
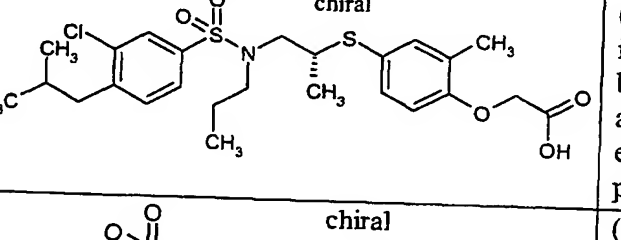
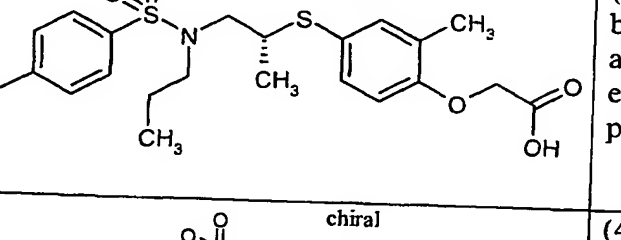
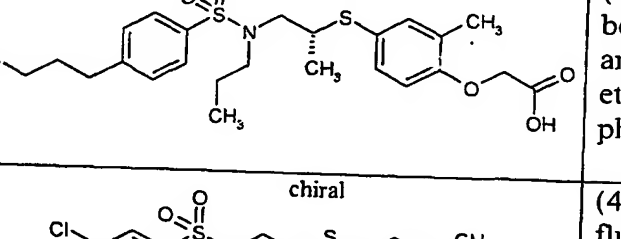
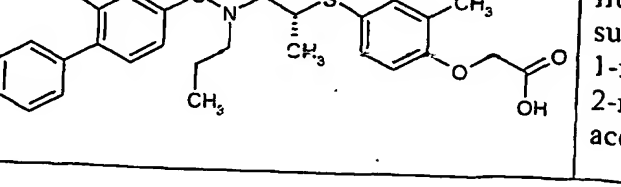
No.	Structure	Name
36		(R)-(4-{2-[(6-Chloro-5-fluoro-3-methylbenzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
37		(4-{2-[(4-Bromobenzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
38		(4-{2-[(3,4-Dichlorobenzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
39		(4-{2-[(4-Isopropylbenzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
40		(2-Methyl-4-{2-[(4-pentylbenzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
41		(4-{2-[(2-Chloro-4-trifluoromethylbenzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
42		(2-Methyl-4-{2-[propyl-(3-trifluoromethylbenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

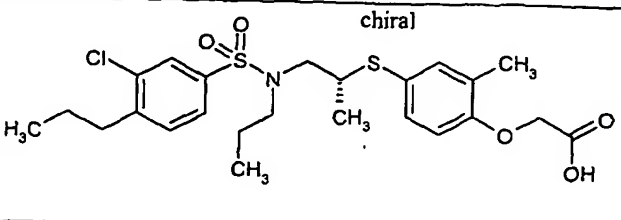
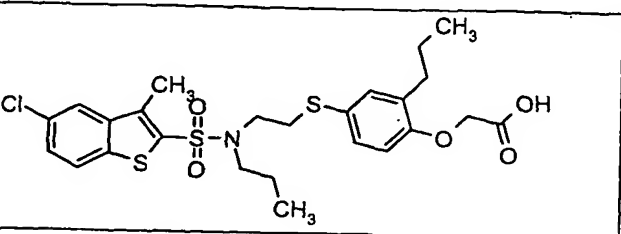
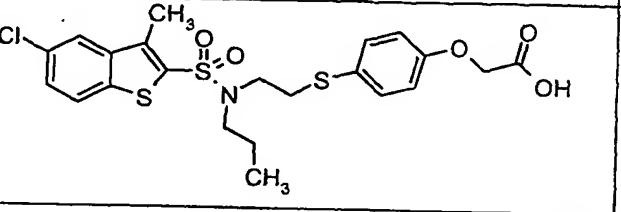
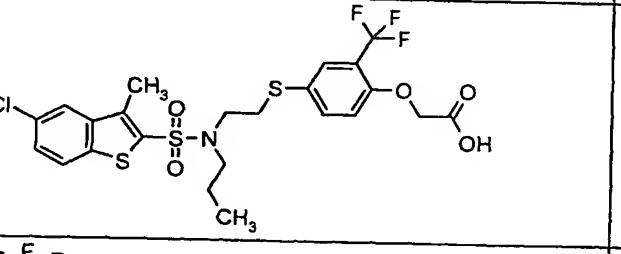
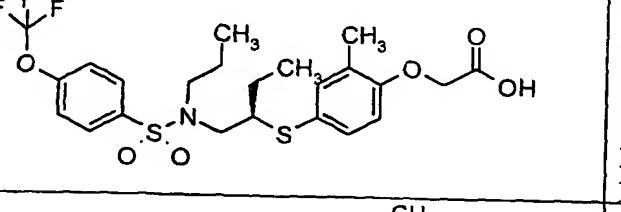
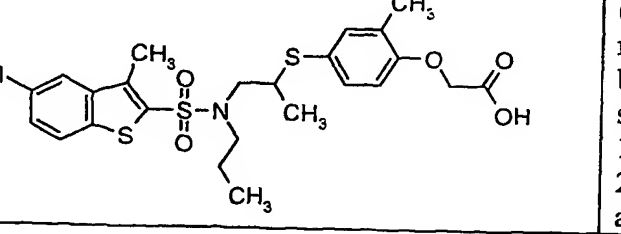
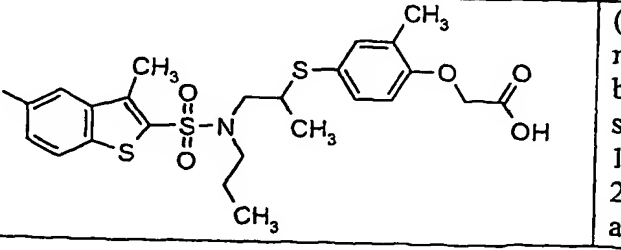
No.	Structure	Name
43		(4-{2-[(4-Bromo-2-methyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
44		(4-{2-[(3,4-Dibromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
45		(2-Methyl-4-{2-[propyl-(4-propyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
46		(4-{2-[(2,4-Dichloro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
47		(4-{2-[(4-Iodo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
48		(4-{2-[(3-Chloro-4-methyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
49		(4-{2-[(4-Bromo-2,5-difluoro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

No.	Structure	Name
50		(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
51		(4-{2-[(3,4-Dichloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
52		(2-Methyl-4-{2-[propyl-(2'-trifluoromethyl-biphenyl-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
53		(2-Methyl-4-{2-[propyl-(3'-trifluoromethyl-biphenyl-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
54		(2-Methyl-4-{2-[propyl-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
55		(4-{2-[(2'-Fluoro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
56		(4-{2-[(4'-Fluoro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

No.	Structure	Name
57		(2-Methyl-4-{2-[propyl-(4'-trifluoromethoxy-biphenyl-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
58		(4-{2-[(3',4'-Dichloro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid
59		(4-{2-[(3'-Fluoro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid
60		(4-{2-[(2'-Chloro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid
61		(4-{2-[(4'-Methoxy-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid
62		(4-{2-[(4'-Methoxy-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid
63		(4-{2-[(3'-Chloro-4'-fluoro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid

No.	Structure	Name
64		(4-{2-[(4-Chloro-3-trifluoromethyl)-benzenesulfonyl]-propyl-amino}-ethylsulfanyl)-2-methyl-phenoxy)-acetic acid
65		(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
66		(2-Methyl-4-{1-methyl-2-[propyl-(4-propyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
67		(4-{2-[(4-Chloro-3-trifluoromethyl)-benzenesulfonyl]-propyl-amino]-1-methyl-ethylsulfanyl)-2-methyl-phenoxy)-acetic acid
68		(4-{2-[(3-Chloro-4-trifluoromethyl)-benzenesulfonyl]-propyl-amino]-1-methyl-ethylsulfanyl)-2-methyl-phenoxy)-acetic acid
69		(4-{2-[(4-Butyl)-benzenesulfonyl]-propyl-amino}-ethylsulfanyl)-2-methyl-phenoxy)-acetic acid
70		(4-{2-[(4-Isobutyl)-benzenesulfonyl]-propyl-amino}-ethylsulfanyl)-2-methyl-phenoxy)-acetic acid

No.	Structure	Name
71		(4-{2-[(2-Chloro-4-trifluoromethyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
72		(4-{2-[(4-Bromo-3-chloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
73		(4-{2-[(4-Butyl-3-chloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
74		(4-{2-[(3-Chloro-4-isobutyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
75		(4-{2-[(4-Bromo-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
76		(4-{2-[(4-Butyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
77		(4-{2-[(2-Chloro-4'-fluoro-biphenyl-4-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

No.	Structure	Name
78		(4-{2-[(3-Chloro-4-propyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
79		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-propyl-phenoxy)-acetic acid
80		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
81		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-trifluoromethyl-phenoxy)-acetic acid
82		[2-Methyl-4-(1-[(propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-methyl)-propylsulfanyl]-phenoxy]-acetic acid
83		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
84		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

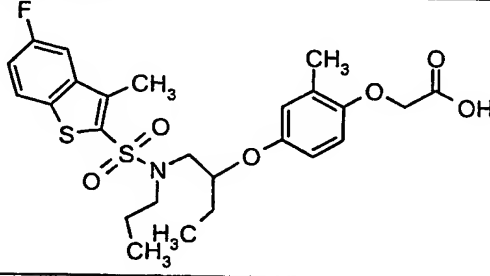
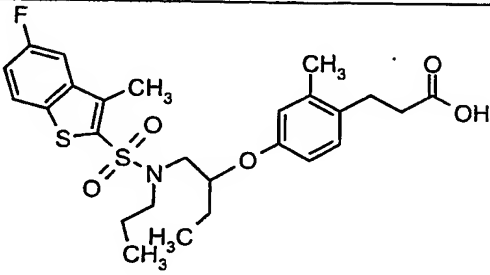
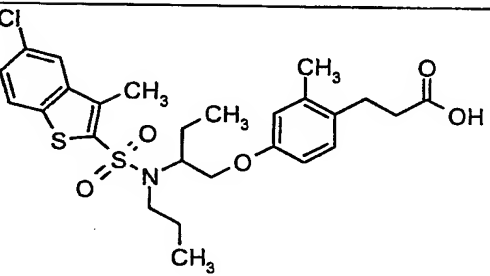
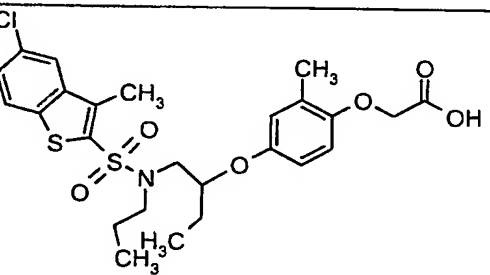
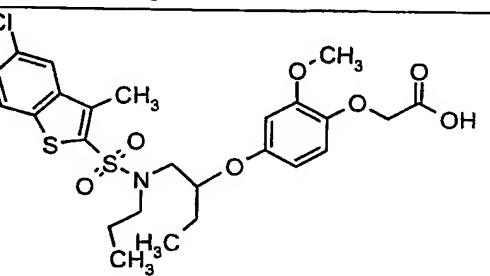
No.	Structure	Name
85		(2-Methyl-4-{2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
86		(2-Methyl-4-{2-[propyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
87		(4-{2-[(4-Ethyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
88		(2-Methyl-4-{2-[(2-methyl-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
89		(2-Methyl-4-{2-[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

No.	Structure	Name
90		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
91		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3-methyl-butyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
92		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclopropyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
93		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclobutyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
94		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclopropylmethyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
95		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-pentyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

No.	Structure	Name
96		(4-{2-[(5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid
97		(4-{2-[(Biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid
98		(4-{2-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methylphenylsulfanyl)-acetic acid
99		(4-{3-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-2-methylphenoxy)-acetic acid
100		(4-{2-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methylphenoxy)-acetic acid
101		3-(4-{2-[(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenyl)-propionic acid

No.	Structure	Name
102		2-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-2-methyl-propionic acid
103		3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methoxy-phenyl)-propionic acid
104		(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
105		3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenyl)-propionic acid
106		(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid
107		(2-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

No.	Structure	Name
108		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-ethyl-phenoxy)-acetic acid
109		(2-Methyl-4-{2-[(naphthalene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid
110		(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
111		[3-Chloro-4-(1-{[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-methyl}-propylsulfanyl)-phenyl]-acetic acid
112		(R)-(3-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-phenyl)-acetic acid
113		(3-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenyl)-acetic acid

No.	Structure	Name
114		[4-(1-{{(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-2-methyl-phenoxy]-acetic acid
115		3-[4-(1-{{(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-2-methyl-phenyl]-propionic acid
116		3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-butoxy}-2-methyl-phenyl)-propionic acid
117		[4-(1-{{(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-2-methyl-phenoxy]-acetic acid
118		[4-(1-{{(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-2-methoxy-phenoxy]-acetic acid

No.	Structure	Name
119		(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
120		(4-{2-[Benzyl-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid
121		[4-(1-{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid

Also encompassed by the present invention is a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and at least one compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Also encompassed by the present invention is a pharmaceutical composition comprising: (1) at least one of compound of the present invention or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof; (2) a second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α -glucosidase inhibitors, insulin secretagogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin; and (3) a pharmaceutically acceptable carrier.

Also encompassed by the present invention is a method of modulating a peroxisome proliferator activated receptor (PPAR), comprising the step of contacting the receptor with at least one compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

5 The method recited above, wherein the PPAR is a gamma-receptor.

 The method recited above, wherein the PPAR is a delta-receptor.

 The method recited above, wherein the PPAR is a gamma and delta receptor.

10 Also encompassed by the present invention is a method for treating or preventing a PPAR-gamma mediated disease or condition in a mammal comprising the step of administering an effective amount of at least one compound of the present invention.

15 Also encompassed by the present invention is a method for treating or preventing a PPAR-delta mediated disease or condition in a mammal comprising the step of administering an effective amount of at least one compound of the present invention.

 Also encompassed by the present invention is a method for treating or preventing a PPAR-gamma and delta mediated disease or condition in a mammal comprising the step of administering an effective amount of at least one compound of the present invention.

20 Also encompassed by the present invention is a method for lowering blood-glucose in a mammal comprising the step of administering an effective amount of at least one compound of the present invention.

25 Also encompassed by the present invention is a method of treating or preventing disease or condition in a mammal selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of a compound of at least one
30 compound of the present invention.

Also encompassed by the present invention is a method of treating or preventing diabetes mellitus in a mammal comprising the step of administering to a mammal a therapeutically effective amount of at least one compound of the present invention.

5 Also encompassed by the present invention is a method of treating or preventing cardiovascular disease in a mammal comprising the step of administering to a mammal a therapeutically effective amount of at least one compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

10 Also encompassed by the present invention is a method of treating or preventing syndrome X in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

Also encompassed by the present invention is a method of treating or preventing disease or condition in a mammal selected from the group consisting of
15 hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of at least one compound of the
20 present invention, and an effective amount of second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α -glucosidase inhibitors, insulin secretagogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents,
25 fibrates, vitamins and aspirin.

Also encompassed by the present invention is use of a compound of the present invention and pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, for the manufacture of a medicament for the treatment of a condition modulated by a PPAR.

The terms used to describe the present invention have the following meanings unless otherwise indicated.

As used herein, the term "aliphatic" or "aliphatic group" is a non-aromatic, consisting solely of carbon and hydrogen and may optionally contain one or more units of saturation, e.g., double and/or triple bonds (also refer herein as "alkenyl" and "alkynyl"). An aliphatic or aliphatic group may be straight chained, branched (also refer herein as "alkyl") or cyclic (also refer herein as "cycloalkyl"). When straight chained or branched, an aliphatic group typically contains between about 1 and about 10 carbon atoms, more typically between about 1 and about 6 carbon atoms. When cyclic, an aliphatic typically contains between about 3 and about 10 carbon atoms, more typically between about 3 and about 7 carbon atoms. Aliphatics are preferably C₁-C₁₀ straight chained or branched alkyl groups (i.e. completely saturated aliphatic groups), more preferably C₁-C₆ straight chained or branched alkyl groups. Examples include, but are not limited to methyl, ethyl, propyl, n-propyl, iso-propyl, n-butyl, sec-butyl, and tert-butyl. Additional examples include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, cyclopentyl, cyclohexyl and the like.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups of a designated number of carbon atoms of either a straight or branched saturated configuration. Examples of "alkyl" include, but are not limited to: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl, pentyl, hexyl, isopentyl and the like. Alkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "alkenyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon double bond, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, alkyl, 2-butenyl and the like. Alkenyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "alkynyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon triple bond, which may occur at any point along the chain. Example of alkynyl is acetylene. Alkynyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "alkyl-alkoxy" represents an alkyl group substituted with alkoxy group as defined above. Example of "alkyl-alkoxy" is $(\text{CH}_2)_n\text{OCH}_3$ ($n=1$ to 6) and the like. Alkyl-alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms, more typically 3 to 6 carbon atoms. Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like. Cycloalkyl as defined above also includes a tricycle, such as adamantyl. Cycloalkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term "haloalkyl" is a $\text{C}_1\text{-C}_6$ alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. Examples of haloalkyl group are trifluoromethyl, CH_2CF_3 and the like.

The term "haloalkyloxy" represents a $\text{C}_1\text{-C}_6$ haloalkyl group attached through an oxygen bridge, such as OCF_3 . The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl). The "aryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from O, N, or S. The heteroaryl as defined above also includes heteroaryl fused with another heteroaryl, aryl fused with heteroaryl or aryl fused with heterocyclyl as defined herein. The "heteroaryl" may also be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heteroaryl are, but are not limited to: furanyl, thienyl (also referred to herein as "thiophenyl"), thiazolyl, imidazolyl, indolyl, isoindolyl, isooxazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnoliny, benzofuranyl, benzothienyl (or benzothiophenyl), benzotriazolyl, benzoxazolyl, quinoline, isoxazolyl, isoquinoline 1,4 benzodioxan, or 2,3-dihydrobenzofuranyl and the like.

The term "bi-aryl" is defined as aryl substituted with another aryl or aryl substituted with heteroaryl as defined above. Examples of "biaryl" are, but are not limited to: bi-phenyl where phenyl is substituted with another phenyl, and phenyl-pyridyl where phenyl is substituted with pyridyl. The "bi-aryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "bi-heteroaryl" is defined as heteroaryl substituted with another heteroaryl, or heteroaryl substituted with aryl or biaryl as defined above. Examples of "bi-heteroaryl" are, but are not limited to: thienyl-pyrazolyl, thienyl-thienyl, thienyl-pyridyl, thienyl-phenyl, thienyl-biphenyl and the like. The "bi-heteroaryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "heterocyclyl" refers to a non-aromatic ring which contains one or more heteroatoms selected from O, N or S, which includes a monocyclic, bicyclic or tricyclic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from O, N or S. The "heterocyclyl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heterocyclyl include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine.

The term "carbocyclyl" refers to carbocyclyl ring that is saturated or partially saturated ring. Examples of carbocyclyl are, but not limited to, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl and the like.

An aryl-C₁-C₆-alkyl group, as used herein, is an aryl substituent that is linked to a compound by an alkyl group having from one to six carbon atoms. The aryl-C₁-C₆-alkyl group as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The "aminoalkyl" as used herein contains both a basic amino group (NH₂) and an alkyl group as defined above.

The term R^{6A} (or bioisosteres) as used herein includes carboxamide, C₁-C₃alkylnitrile, sulfonamide, acylsulfonamide and tetrazole, wherein these are optionally substituted with one or more suitable substituents selected from haloalkyl, aryl, heteroaryl, and C₁-C₆ alkyl. The heteroalkyl, aryl, heteroaryl and alkyl may further optionally substituted with one or more substituents selected from the list provided for R¹⁵. The examples of R^{6A} (or bioisosteres) are, but not limited to, hydroxamic acid, acyl cyanamide, tetrazoles, sulfinylazole, sulfonylazole, 3-hydroxyisoxazole, hydroxythiadiazole, sulphonate and acylsulfonamide.

The term "acyl" means a R-C(O)- group where R is C₁-C₆ alkyl or aryl such as phenyl. Preferred acyl groups are those in which the alkyl group is lower alkyl such as acetyl.

The term "active ingredient" means the compounds generically described by Formula I as well as the salts, solvates and prodrugs of such compounds.

The term "pharmaceutically acceptable" means that the carrier, diluents, excipients and salt must be compatible with the other ingredients of the composition, and not deleterious to the recipient thereof. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well-known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein.

"Treating" refers to mediating a disease or condition, and preventing or mitigating its further progression or ameliorating the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of a compound of the present invention, or of its salt, solvate, hydrate or prodrug thereof that will elicit the biological or medical response of a tissue, system or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount, which is sufficient to modulate a PPAR receptor such as a PPAR α , PPAR γ , PPAR δ or PPAR γ/δ receptor to mediate a disease or condition. Conditions mediated by PPAR receptors include, for example, diabetes mellitus, cardiovascular disease, Syndrome X, obesity and gastrointestinal disease. Additional conditions associated with the modulation of a PPAR receptor include inflammation related conditions, which include, for example, IBD (inflammatory bowel disease), rheumatoid arthritis, psoriasis, Alzheimer's disease, Crohn's disease and ischemia reperfusion injury (stroke and myocardial infarction).

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, ~~cattle~~ swine, horses, sheep, dogs, cats, mice, rats and the like.

Administration to a human is most preferred. A human to whom the compounds and compositions of the present invention are administered has a disease or condition in which control blood glucose levels are not adequately controlled without ~~medical~~ intervention, but wherein there is endogenous insulin present in the human's blood. Non-insulin dependent diabetes mellitus (NIDDM) is a chronic disease or

condition characterized by the presence of insulin in the blood, even at levels above normal, but resistance or lack of sensitivity to insulin action at the tissues.

Those skilled in the art will recognize that stereocenters exist in compound of Formula I. Accordingly, the present invention includes all possible stereoisomers and
5 geometric isomers of Formula I including racemic compounds and the optically active isomers.

The compounds of Formula I contain one or more chiral centers and exist in different optically active forms. When compounds of Formula I contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes
10 both enantiomers and mixtures of enantiomers, such as racemic mixtures. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art, for example by formation of diastereoisomeric salts which may be separated by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated by crystallization and gas-liquid or liquid chromatography;
15 selective reaction of one enantiomer with an enantiomer-specific reagent such as enzymatic esterification; and gas-liquid or liquid chromatography in a chiral environment such as on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. See also *Stereochemistry of Carbon Compounds* by E.L. Eliel (Mcgraw Hill, 1962) and *Tables of Resolving Agents* by S. H. Wilen. It will be
20 appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

25 When a compound of Formula I has more than one chiral substituents, it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of Formula I and
30 mixtures thereof.

-55-

Certain compounds of Formula I may exist in different stable conformational forms, which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes
5 each conformational isomer of compounds of Formula I and mixtures thereof.

Certain compound of Formula I may exist in zwitterionic form, and the present invention includes each zwitterionic form of compounds of Formula I and mixtures thereof.

Certain compounds of Formula I and their salts may exist in more than one
10 crystal form. Polymorphs of compounds of Formula I form part of the present invention and may be prepared by crystallization of a compound of Formula I under different conditions, such as using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; and various modes of cooling ranging from very fast to very slow cooling during crystallization. Polymorphs may also
15 be obtained by heating or melting a compound of Formula I followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or other available techniques.

Certain compounds of Formula I and their salts may exist in more than one
20 crystal form, and the present invention includes each crystal form and mixtures thereof.

Certain compounds of Formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of
25 Formula I, which are substantially non-toxic to mammals. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral, organic acid: an organic base or inorganic base. Such salts are known as base addition salts, respectively. It should be recognized that the particular counterion forming a part of any salt of the present invention is not of a critical nature so
30 long as the salt as a whole is pharmaceutically acceptable and the counterion does not contribute undesired qualities to the salt as a whole.

By virtue of its acidic moiety, a compound of Formula I forms salts with pharmaceutically acceptable bases. Some examples of base addition salts include metal salts such as aluminum; alkali metal salts such as lithium, sodium or potassium; and alkaline earth metal salts such as calcium, magnesium, ammonium, or substituted ammonium salts. Examples of substituted ammonium salts include, for instance, those with lower alkylamines such as trimethylamine and triethylamine; hydroxyalkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine; cycloalkylamines such as bicyclohexylamine or dibenzylpiperidine, N-benzyl- β -phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, glucamine, N-piperazine methylglucamine; bases of the pyridine type such as pyridine, collidine, quinine or quinoline; and salts of basic amino acids such as lysine and arginine.

Examples of inorganic bases include, without limitation, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

Compounds of Formula I, which are substituted with a basic group, may exist as salts with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of Formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

The compounds of present invention, which bind to and activate the PPARs, lower one or more of glucose, insulin, triglycerides, fatty acids and/or cholesterol, and are therefore useful for the treatment and/or prevention of hyperglycemia, dyslipidemia and in particular Type II diabetes as well as other diseases including syndrome X, Type I diabetes, hypertriglyceridemia, insulin resistance, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, heart failure, coagulopathy, hypertension, and cardiovascular diseases, especially arteriosclerosis. In addition, these

compounds are indicated to be useful for the regulation of appetite and food intake in subjects suffering from disorders such as obesity, anorexia bulimia and anorexia nervosa.

The compounds and compositions of the present invention are also useful to treat acute or transient disorders in insulin sensitivity, which sometimes occurs following a surgery, trauma, myocardial infarction and the like. The compounds and compositions of the present invention are also useful for lowering serum triglyceride levels. Elevated triglyceride level, whether caused by genetic predisposition or by a high fat diet, is a risk factor for the development of heart disease, stroke, and circulatory system disorders and diseases. The physician of ordinary skill will know how to identify humans who can benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective, non-toxic amount of a compound of Formula I, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycemic human or non-human mammal in need thereof.

The compounds of the present invention are useful as therapeutic substances in preventing or treating Syndrome X, diabetes mellitus and related endocrine and cardiovascular disorders and diseases in human or non-human animals.

The present invention also relates to the use of a compound of Formula I as described above for the manufacture of a medicament for treating a PPAR γ or PPAR δ mediated condition, separately or in combination.

A therapeutically effective amount of a compound of Formula I can be used for the preparation of a medicament useful for treating Syndrome X, diabetes, treating obesity, lowering tryglyceride levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing arteriosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of Formula I of the present invention typically reduces serum glucose levels, more specifically HbA1c, of a patient by about

0.7% or more; typically reduces serum triglyceride levels of a patient by about 20% or more; and increases serum HDL levels in a patient.

Additionally, an effective amount of a compound of Formula I and a therapeutically effective amount of one or more active agents selected from
5 antihyperlipidemic agent, plasma HDL-raising agents, antihypercholesterolemic agents, fibrates, vitamins, aspirin, insulin secretagogues, insulin and the like can be used together for the preparation of a medicament useful for the above described treatments.

Advantageously, compositions containing the compound of Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit
10 containing from about 1 to about 500 mg. It is understood that the amount of the compounds or compounds of Formula I that will be administered is determined by a physician considering of all the relevant circumstances.

Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes,
15 dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes,
20 dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially arteriosclerosis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the present invention may be used effectively alone or in combination with one or more additional active agents depending
25 on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition, which contains a compound of Formula I and one or more additional active agents, as well as administration of a compound of Formula I and each active agent in its own separate pharmaceutical dosage. For example, a compound of Formula I or thereof and an insulin secretagogue such as biguanides,
30 thiazolidinediones, sulfonylureas, insulin or α -glucosidase inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage s. Where separate dosage s are used, a

compound of Formula I and one or more additional active agents can be administered at essentially the same time, i.e., concurrently or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

5 An example of combination treatment or prevention of arteriosclerosis may involve administration of a compound of Formula I or salts thereof in combination with one or more of second active therapeutic agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin and the like. As noted above, the compounds of Formula I can be administered in combination with more than one additional active agent.

10 Another example of combination therapy can be seen in treating diabetes and related disorders wherein the compounds of Formula I or salts thereof can be effectively used in combination with second active therapeutic, such as sulfonylureas, biguanides, thiazolidinediones, α -glucosidase inhibitors, other insulin secretagogues, insulin as well as the active agents discussed above for treating arteriosclerosis.

15 The examples of second therapeutic agents are insulin sensitizers, PPAR γ agonists, glitazones, troglitazone, pioglitazone, englitazone, MCC-555, BRL 49653, biguanides, metformin, phenformin, insulin, insulin mimetics, sulfonylureas, tolbutamide, glipizide, alpha-glucosidase inhibitors, acarbose, cholesterol lowering agent, HMG-CoA reductase inhibitors, lovastatin, simvastatin, pravastatin, fluvastatin, 20 atorvastatin, rivastatin, other statins, sequestrates, cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran, nicotinic alcohol, nicotinic acid: a nicotinic acid salt, PPAR α agonists, fenofibric acid derivatives, gemfibrozil, clofibrate, fenofibrate, benzaifibrate, inhibitors of cholesterol absorption, beta-sitosterol, acyl CoA:cholesterol acyltransferase inhibitors, melinamide, probucol, PPAR δ agonists, 25 antiobesity compounds, fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, and ileal bile acid transporter inhibitors.

The compounds of the present invention and the pharmaceutically acceptable salts, solvates and hydrates thereof have valuable pharmacological properties 30 and can be used in pharmaceutical compositions containing a therapeutically effective amount of a compound of the present invention, or pharmaceutically acceptable salts,

-60-

esters or prodrugs thereof, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional
5 adjuvants. Proper is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the active ingredient, which is a compound of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose suitable for
10 administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically acceptable excipients. The quantity of active ingredient in a unit dose may be varied or
15 adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts considering various factors, such as without limitation, the species, age, weight, sex, medical condition of the
20 recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses of two,
25 three or more times per day. Where delivery is via transdermal forms, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eye drop, rectal, transmucosal, topical or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular,
30 subcutaneous, intramedullary injections, as well as intrathecal, direct intraven-tricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the

present invention can also be administered in a targeted drug delivery system, such as in a liposome coated with endothelial cell-specific antibody.

For oral administration, the compounds of the present invention can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the present invention to be Formulated as tablets, pills, powders, sachets, granules, dragees, capsules, liquids, elixirs, tinctures, gels, emulsions, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

For oral administration in the form of a tablet or capsule, the active ingredient may be combined with an oral, non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, methyl cellulose, calcium carbonate, calcium phosphate, calcium sulfate, sodium carbonate, mannitol, sorbitol, and the like; together with, optionally, disintegrating agents, such as, without limitation, cross-linked polyvinyl pyrrolidone, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid: or a salt thereof such as sodium alginate, and the like; and, optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethyl-cellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid: sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Solid forms include powders, tablets and capsules. A solid carrier can be one or more substances, which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

In powders, the carrier is a finely divided solid, which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile liquids include suspensions, emulsions, syrups, and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations, which can be used orally, include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

All formulations for oral administration should be in dosages suitable for such administration. Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules.

For parental administration, the compounds of the present invention or salts thereof can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. Formulations for injection may be presented in unit dosage form, such as in ampoules or in multi-dose container with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that each syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against any contamination. The carrier can be solvent or dispersion medium containing, for example, water, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

For buccal administration, the compositions may take the form of tablets or lozenges Formulated in a conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of a dry powder inhaler, or an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered

-64-

amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Pharmaceutical compositions of the present invention can be manufactured
5 in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

In making the compositions of the present invention, the active
10 ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, lyophilized solid or paste, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing for example up to
15 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

In yet another embodiment of the present invention, the compound is radiolabelled, such as with carbon-14 or tritiated. Said radiolabelled or tritiated
20 compounds are useful as reference standards for in vitro assays to identify new PPAR γ/δ agonists.

Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPAR γ , PPAR α and PPAR δ receptors are determined by the procedures detailed below. DNA-dependent
25 binding (ABCD binding) is carried out using Scintillation Proximity Assay (SPA) technology with PPAR receptors. Tritium-labeled PPAR α and PPAR γ agonists are used as radioligands for generating displacement curves and IC₅₀ values with compounds of the present invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contains an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the
30 luciferase reporter cDNA. Appropriate PPARs and RXR α are constitutively expressed using plasmids containing the CMV promoter. Since for PPAR α and PPAR β ,

interference by endogenous PPAR γ in CV-1 cells is an issue, in order to eliminate such interference, a GAL4 chimeric system is used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Receptor activation by compounds of the present invention is determined relative to PPAR α agonist and PPAR γ agonist reference molecules to obtain percent efficacies. EC₅₀ values are determined by computer fit to a concentration-response curve. A typical range for concentration determination is from 1nM to 10 μ M. For binding or cotransfection studies with receptors other than PPARs, similar assays are carried out using appropriate ligands, receptors, reporter constructs and etc. for that particular receptor. In some cases, a single high concentration of agonist (10 μ M) was used.

These studies are carried out to evaluate the ability of compounds of the present invention to bind to and/or activate various nuclear transcription factors, particularly huPPAR α ("hu" indicates "human"), huPPAR γ and huPPAR δ . These studies provide in-vitro data concerning efficacy and selectivity of compounds of the present invention. Furthermore, binding and cotransfection data for compounds of the present invention are compared with corresponding data for reference compounds that act on either huPPAR α or huPPAR γ . The typical range of concentration for binding is from 1nM to 10 μ M. The concentration of test compound required to effect 50% maximal activation of PPAR α (IC_{50 α}) and PPAR γ (IC_{50 γ}) is determined. The compounds of the present invention are, in general, found to have IC₅₀ or EC₅₀ in the range of about 1nM to about 5 μ M for PPAR alpha, gamma or delta.

Evaluation of Triglyceride and Cholesterol Level in HuapoAI Transgenic Mice

Five to six week old male mice, transgenic for human apoAI [C57Bl/6-tgn(apoai)1rub, Jackson Laboratory, Bar Harbor, ME] are housed five per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5001) and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed and assigned to groups based on body weight. Beginning the following morning, mice are dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments are test compounds (30 mg/kg), a positive control

-66-

(fenofibrate, 100 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.2 ml/mouse]. Prior to termination on day 7, mice are weighed and dosed. Three hours after dosing, animals are anesthetized by inhalation of isoflurane (2-4%) and blood obtained via cardiac puncture (0.7-1.0 ml). Whole blood is transferred to serum separator
5 tubes (Vacutainer SST), chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for triglycerides, total cholesterol, compound levels and serum lipoprotein profile by fast protein liquid chromatography (FPLC) coupled to an inline detection system. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

10 The animals dosed with vehicle have average triglycerides values of about 60 to 80 mg/dl, which are reduced by the positive control fenofibrate (33-58 mg/dl with a mean reduction of 37%). The animals dosed with vehicle have average total serum cholesterol values of about 140 to 180 mg/dl, which are increased by fenofibrate (about 190 to 280 mg/dl with a mean elevation of 41%). When subject to FPLC analysis, pooled
15 sera from vehicle-treated hu apoA1 transgenic mice have a high-density lipoprotein cholesterol (HDLc) peak area, which ranges from 47v-sec to 62v-sec. Fenofibrate increases the amount of HDLc (68-96v-sec with a mean percent increase of 48%). Test compounds evaluated in terms of percent increase in the area under the curve.

Representative compounds of the present invention are tested using the above methods or
20 substantially similar methods.

Evaluation of Glucose Levels in db/db Mice

Five week old male diabetic (db/db) mice [C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates (db+) are housed 6 per cage
25 (10"x20"x8" with aspen chip bedding) with food (Purina 5015) and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized
30 capillary tube balanced on the edge of the bench. Sample is discharged into a heparinized microtainer with gel separator (VWR) and retained on ice. Plasma is obtained after centrifugation at 4°C and glucose is measured immediately. Remaining plasma is frozen

-67-

until the completion of the experiment, and glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights.

Beginning the following morning, mice are dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) for about 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After 24 hour bleed, animals are weighed and dosed for the final time. Three hours after dosing on day 8, animals are anesthetized by inhalation of isoflurane, and blood obtained is via cardiac puncture (0.5-0.7 ml). Whole blood is transferred to serum separator tubes, chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

The animals dosed with vehicle have average triglycerides values of about 170 to 230 mg/dl, which are reduced by the positive PPAR γ control (about 70 to 120 mg/dl with a mean reduction of 50%). Male db/db mice are hyperglycemic (average glucose of about 680 to 730 mg/dl on the 7th day of treatment), while lean animals have average glucose levels between about 190 and 230 mg/dl. Treatment with the positive control agent reduces glucose significantly (about 350 to 550 mg/dl with a mean decrease towards normalization of 56%).

Glucose is measured colorimetrically by using commercially purchased reagents (Sigma #315-500). According to the manufacturers, the procedures are modified from published work (McGowan et al. *Clin Chem.* 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte coupled with a color reaction first described by Trinder (Trinder, *P. Ann Clin Biochem*, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified for use in a 96 well format. Standards (Sigma #339-11, Sigma #16-11, and Sigma #CC0534 for glucose, triglycerides and total cholesterol, respectively), quality control plasma (Sigma # A2034),

-68-

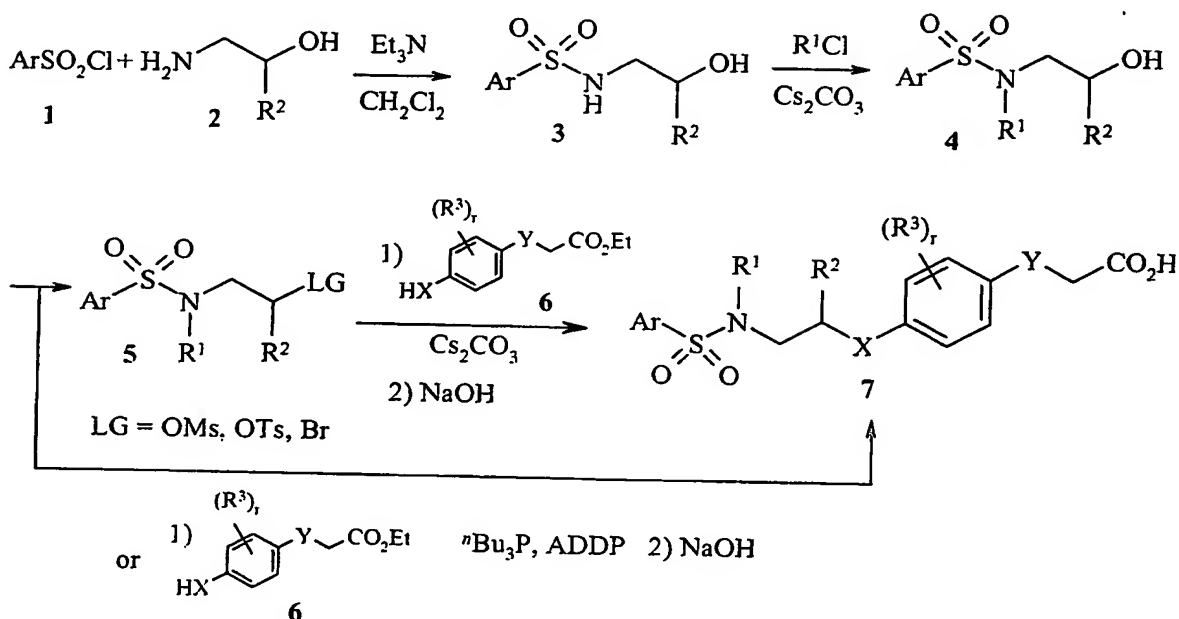
and samples (2 or 5 μ l/well) are measured in duplicate using 200 μ l of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 μ l water, provided a blank for each specimen. Plates are incubated at room temperature (18, 15, and 10 minutes for glucose, triglycerides and total cholesterol, respectively) on a plate shaker and absorbance read at 500 nm (glucose and total cholesterol) or 540 nm (triglycerides) on a plate reader. Sample absorbance is compared to a standard curve (100-800, 10-500, and 100-400 mg/dl for glucose, triglycerides and total cholesterol, respectively). Values for the quality control sample are consistently within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol is quantitated with an in-line detection system. Sample is applied to a Superose® 6 HR 10/30-size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16 ml/min is mixed with the column effluent through a T-connection, and the mixture is passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37°C water bath. The colored product produced in the presence of cholesterol is monitored in the flow stream at 505 nm, and the analog voltage from the monitor is converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration is plotted against time, and the area under the curve corresponding to the elution of VLDL, LDL and HDL is calculated (Perkin Elmer Turbochrome software).

The compounds of the present invention can be prepared according to the procedures of the following schemes and examples, which may further illustrate details for the preparation of the compounds of the present invention. The compounds illustrated in the schemes and examples are, however, not to be construed as forming the only genus that is considered as the present invention.

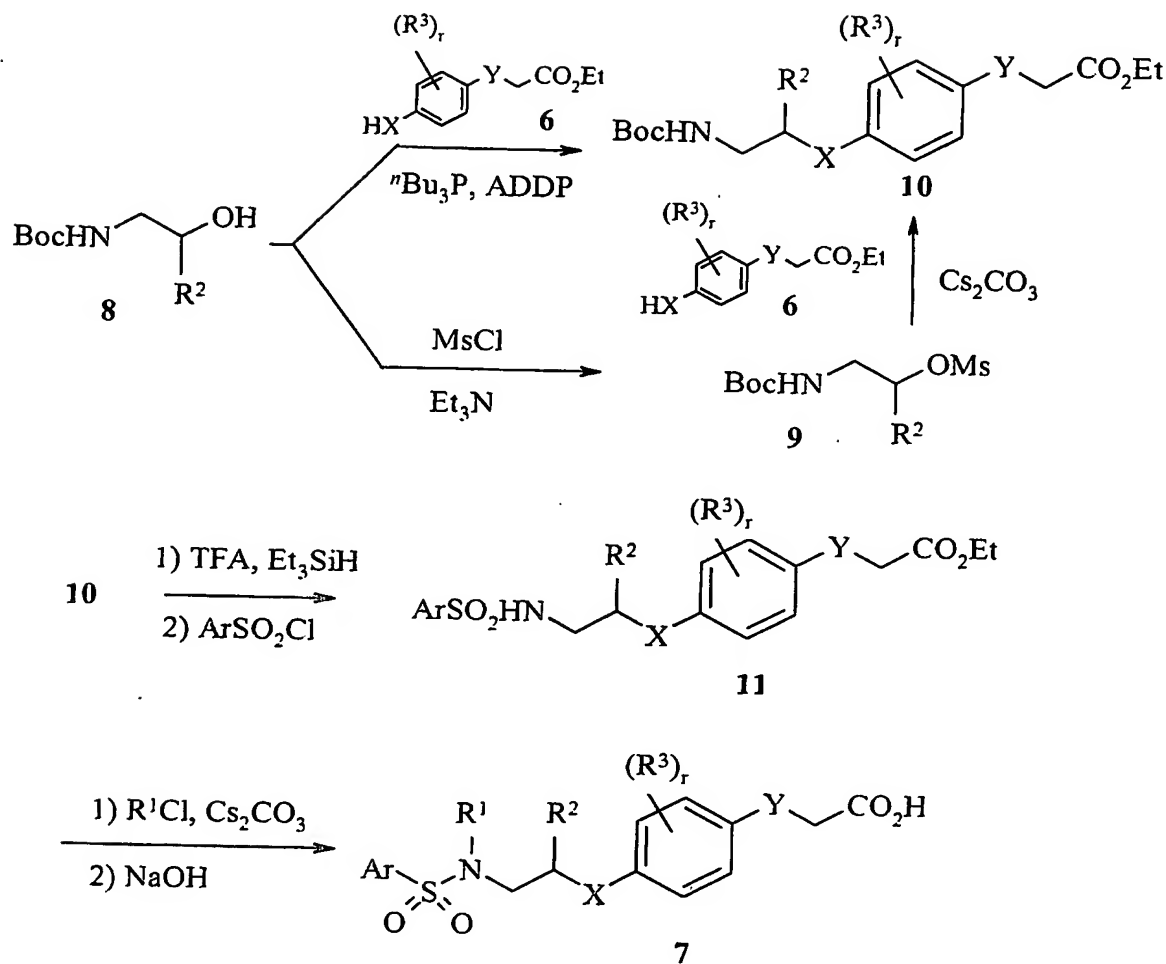
General Reaction Scheme

The compounds of the present invention, in general, may be prepared according to the Reaction Schemes described below.

5 Reaction Scheme 1

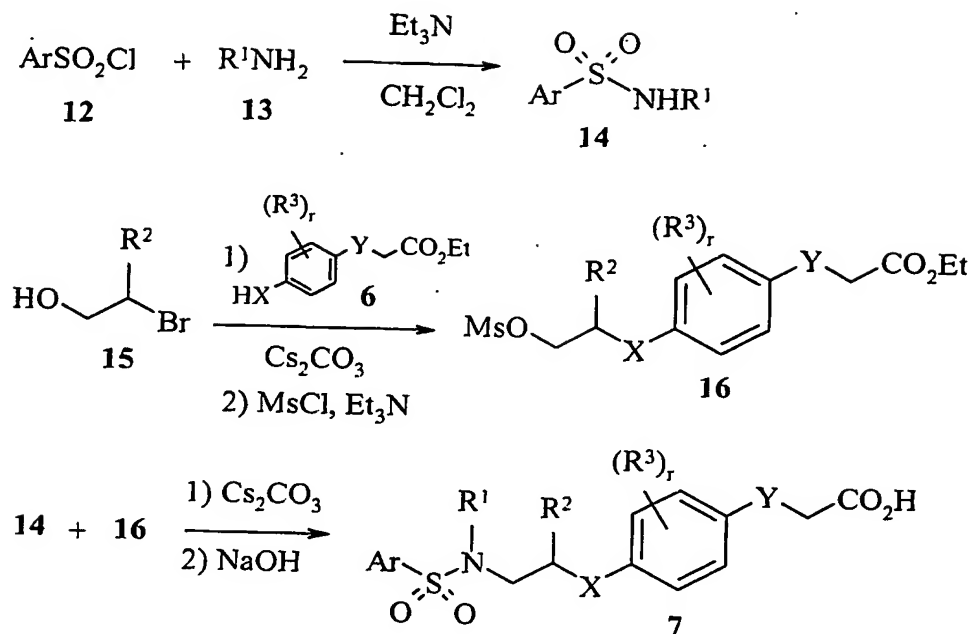
As shown in Reaction Scheme 1, a secondary sulfonamide 3 can be readily prepared from amino alcohol 2 treated with sulfonylchloride 1. Alkylation of 3 with alkyl halide (R^1X , where X is Br or Cl) provides alcohol 4, which is then converted to mesylate, tosylate or bromide 5. A nucleophilic substitution of 5 with phenol (or thiophenol) 6 followed by a hydrolysis yield the acid product 7. Alternatively, the acid 7 can be prepared by coupling alcohol 4 with phenol (thiophenol) 6 under a Mitsunobu reaction condition followed by the hydrolysis.

-70-

Reaction Scheme 2

- 5 As shown in Reaction Scheme 2, a compound **10** can be prepared from alcohol **8** and phenol **6** under a Mitsunobu reaction condition. Alternatively, it can also be prepared from the S_N2 displacement of mesylate **9** with phenol **6**. The mesylate **9** can be easily accessed from the parent alcohol **8** under the standard mesylation condition. The removal of the protecting group such as Boc group under the acidic condition followed by sulfonylation provides the sulfonamide **11**. The N-alkylation using alkyl halide (R¹X, where X is Br or Cl) and subsequent hydrolysis afford the acid compound **7**.
- 10

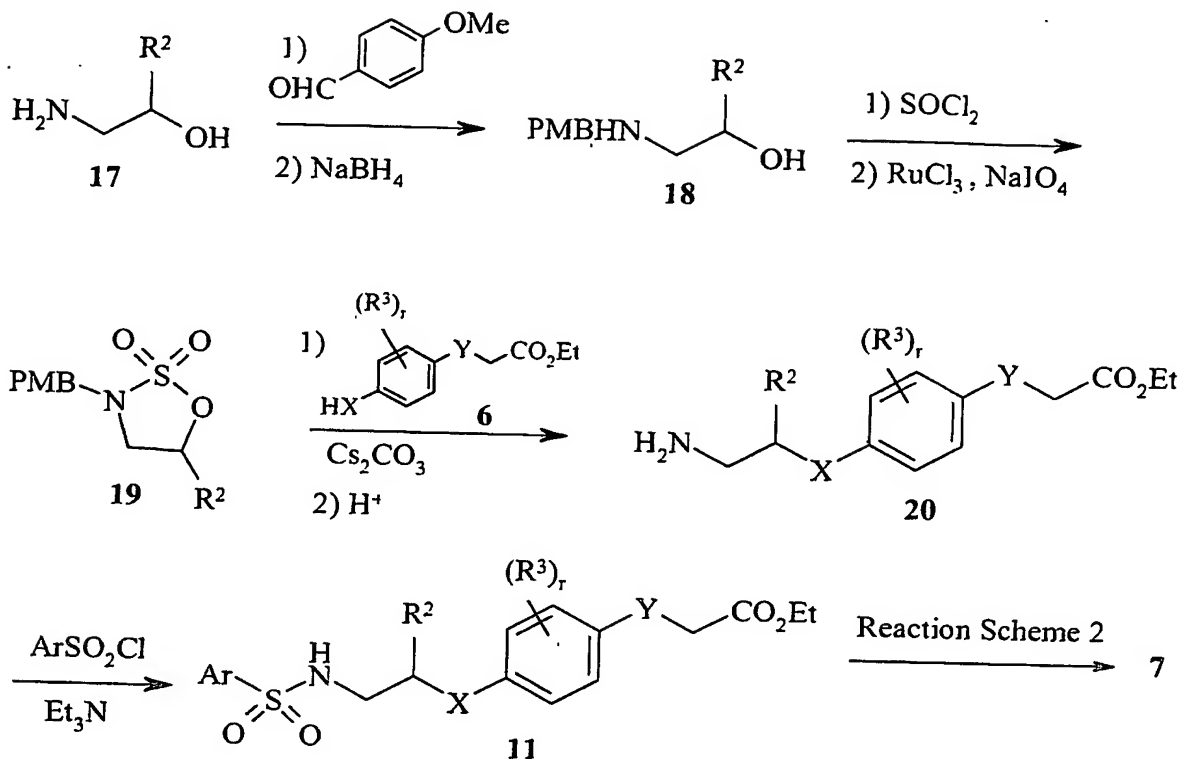
-71-

Reaction Scheme 3

5

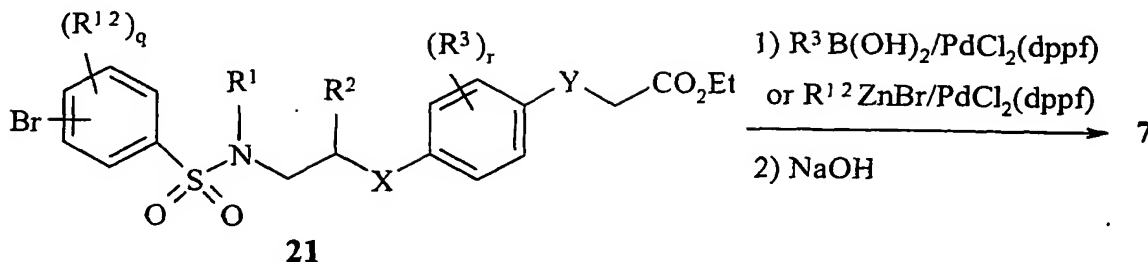
As shown in Reaction Scheme 3, the sulfonamide compound **14** can be prepared from sulfonyl chloride **12** and amine **13**. Subsequent treatment of **14** with mesylate **16** followed by a saponification affords the acid compound **7**. Mesylate **16**, as shown above can be prepared by a S_N2 displacement of bromide **15** with phenol **6**.

10

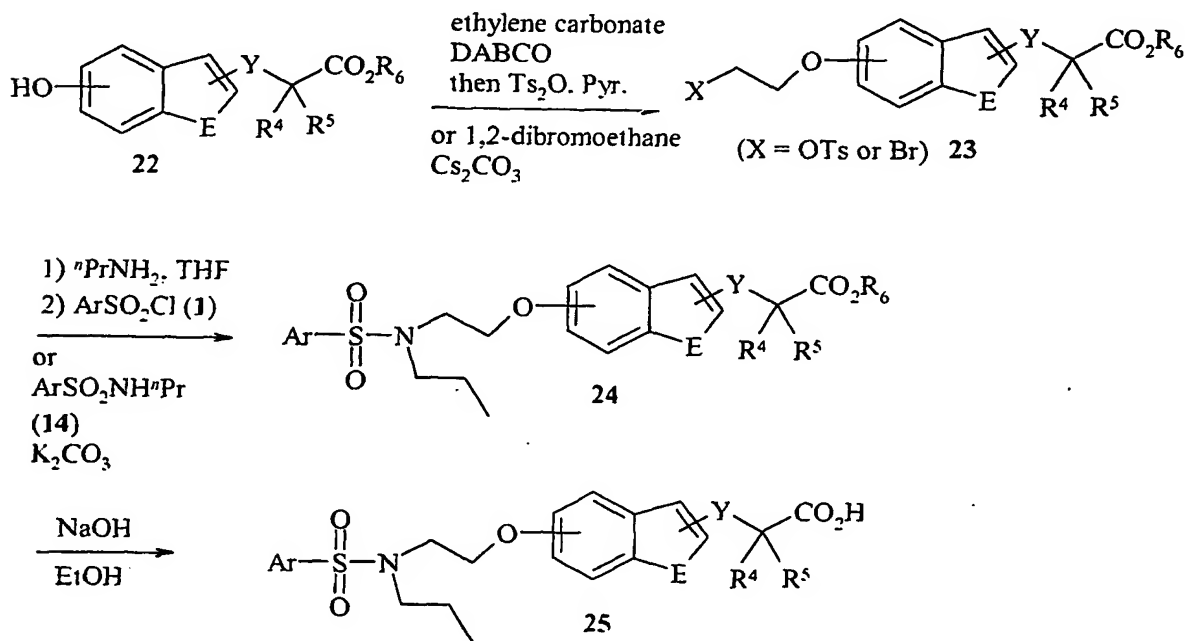
Reaction Scheme 4

- 5 Reaction Scheme 4 illustrates another way to prepare the sulfonamide compound 7. A standard reductive amination converts 17 to amine 18. Cyclic sulfamidate 19 is achieved using a two-step procedure, which involves the formation of sulfamidite followed by oxidation in the presence of catalyst such as RuCl_3 . Nucleophilic ring opening of sulfamidate with phenol 6 followed by a subsequent acid workup affords the amine compound 20. The compound 20 is further converted to sulfonamide 11 under a standard sulfonylation condition. The compound 11 is then converted to the acid compound 7 using the same procedure as described in Reaction Scheme 2.
- 10

-73-

Reaction Scheme 5

- 5 As shown in Reaction Scheme 5, sulfonamide compound **21** is prepared according to the method illustrated in Reaction Scheme 2. Various substitutions are introduced under palladium (Pd) mediated Suzuki and Negishi coupling conditions where a subsequent hydrolysis affords the acid compound **7**.

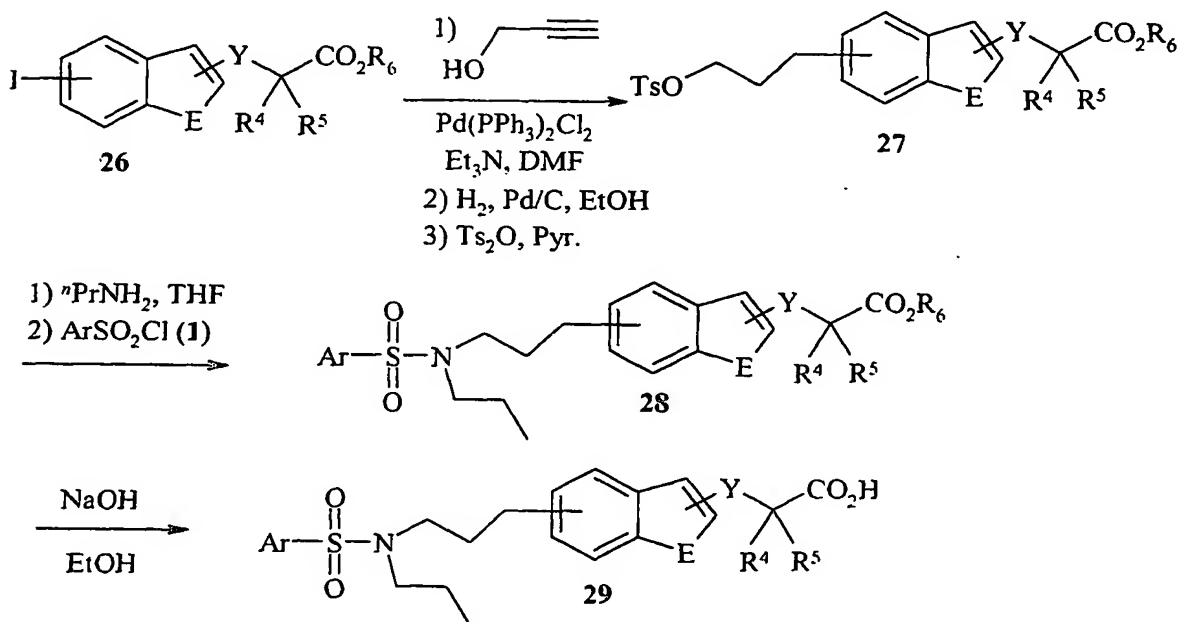
10 Reaction Scheme 6

- 15 Reaction Scheme 6 illustrates a synthetic route to prepare sulfonamide compound **25**. Phenol **22** can be treated with ethylene carbonate followed by a tosylation of the alcohol to afford compound **23**. Alternatively, compound **23** can be obtained in a one step process by treating phenol **22** with 1,2-dibromoethane. Compound **23** is then

-74-

converted to the secondary amine, which is treated with sulfonyl chloride (1) to afford ester 24. Compound 24 can also be obtained by treatment of 23 with arylsulfonamide (14) under a basic condition. Compound 24 undergoes a hydrolysis to afford acid product 25.

5

Reaction Scheme 7

10

Reaction Scheme 7 illustrates a synthetic route to prepare sulfonamide compound 29. A palladium mediated coupling of aryl iodide 26 with propargyl alcohol provides a carbon-carbon bond formation, where the triple bond is reduced under the hydrogenation condition and alcohol is converted to its corresponding tosylate to provide compound 27. Compound 27 is converted to the secondary amine, which is then treated with sulfonyl chloride (1) to afford ester 28. Ester 28 undergoes a hydrolysis to afford acid product 29.

15

-75-

In the Schemes, Procedures and Examples below, various reagent symbols and abbreviations have the following meanings.

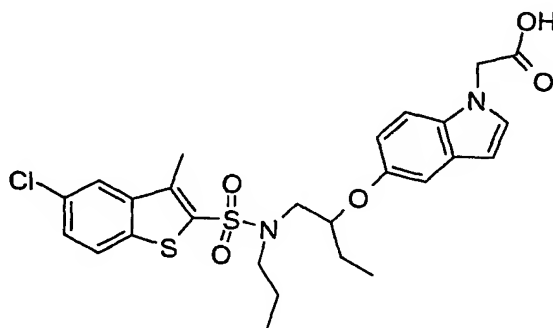
	BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
	Boc	t-butoxycarbonyl
5	CBZ	benzyloxycarbonyl
	DCM	dichloromethane
	DEAD	diethyl azodicarboxylate
	DI	deionized
	DIAD	diisopropyl azodicarboxylate
10	DIPEA	diisopropylethylamine
	DMAP	4-dimethylamino pyridine
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
	eq. (equiv)	equivalent(s)
15	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl
	ESI-MS	electron spray ion-mass spectroscopy
	Et	ethyl
	EtOAc	ethyl acetate
	Fmoc	9-Fluorenylmethyl carbamate
20	h	hours
	HOAc	acetic acid
	HPLC	high performance liquid chromatography
	HRMS	high resolution mass
	h	hour(s)
25	LRMS	low resolution mass
	LAH	lithium aluminum hydride
	Me	methyl
	Ms	methanesulfonyl
	NBS	N-bromosuccinimide
30	Pd ₂ (dba) ₃	tris(dibenzylideneacetone) dipalladium(0)
	Ph	phenyl
	Pr	propyl

-76-

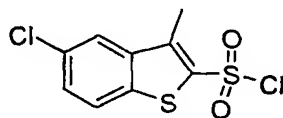
r.t. (RT)	room temperature
TBAF	tetrabutylammonium fluoride
TBS	tertbutyldimethylsilyl
TFA	trifluoroacetic acid
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin-layer chromatography

Example 1

[5-(1-{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-indol-1-yl]-acetic acid

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride :

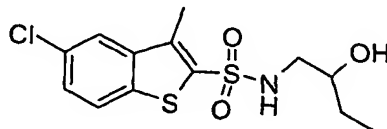


Chlorosulphonic acid (21.8 mL, 0.328mol) was added via syringe to 0°C dichloroethane (118 mL). 5-chloro-3-methylbenzothiophene (20.0 g, 0.109mol) in dichloroethane (32 mL) was added dropwise to the solution. The resulting cranberry-colored solution was thickened to a slurry, which was stirred at room temperature. After 2h, the reaction slurry was poured over an ice/water bath. The resulting precipitate was washed with copious amounts of water and dried overnight in a vacuum oven to provide 26.0 g (84%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, 1H, J = 8.6 Hz), 7.75 (d, 1H, J = 2.0 Hz), 7.35 (dd, 1H, J = 8.6 Hz, 2.0 Hz), 2.45 (s, 3H). R_f = 0.53 in 33% acetone in hexanes.

-77-

Step B

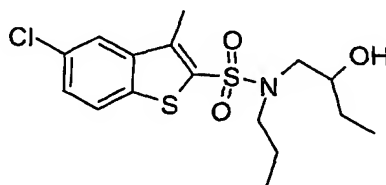
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-amide



The compound of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (2.03 g, 7.22 mmol) in dichloromethane (20 mL) was added dropwise to a 0°C solution of 1-amino-2-butanol (0.8 mL, 9.94 mmol) and triethylamine (2.0 mL, 14.4 mmol) in dichloromethane (80 mL). The resulting solution was stirred at ambient temperature for 1h, then diluted with dichloromethane and washed with water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to provide a quantitative yield of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, 1H, *J* = 8.0 Hz), 7.45 (dd, 1H, *J* = 8.0 Hz, 1.8 Hz), 3.69-3.64 (m, 1H), 3.24 (dd, 1H, *J* = 13.3 Hz, 3.1 Hz), 3.92 (dd, 1H, *J* = 13.3 Hz, 8.0 Hz), 2.66 (s, 3H), 1.53-1.41 (m, 2H), 0.91 (t, 3H, *J* = 7.1 Hz). MS [EI+] 334 (M+H)⁺. R_f = 0.52 in 50% acetone in hexanes.

Step C

15 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-propyl-amide



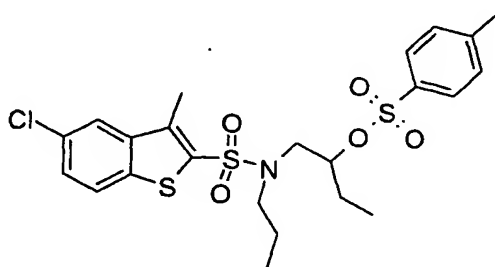
A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-amide (2.41 g, 7.22 mmol) and 1-iodopropane (0.92 mL, 9.38 mmol) in dimethylformamide (120 mL) was treated with cesium carbonate (3.06 g, 9.38 mmol). The resulting mixture was heated to 50°C under N₂ until all of the 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-amide was consumed. The mixture was cooled to ambient temperature and diluted with diethyl ether. The organic layer was washed with 1N HCl and water, dried over Na₂SO₄, and concentrated *in vacuo*. The crude material was purified by flash chromatography, using 20% acetone in hexanes as eluent, to provide 2.43 g (90%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (D, 1h, *J* = 2.3 Hz), 7.74 (d, 1H, *J* = 8.7 Hz), 7.46 (dd, 1H, *J* = 8.7 Hz, 2.3 Hz), 3.83-

-78-

3.76 (m, 1H), 3.35-3.16 (m, 4H), 2.69 (s, 3H), 2.33 (d, 1H, $J = 3.6$ Hz), 1.67-1.57 (m, 2H), 1.53-1.42 (m, 2H), 0.98 (t, 3H, $J = 7.3$ Hz), 0.82 (t, 3H, $J = 7.3$ Hz). MS [EI+] 376 (M+H)⁺. $R_f = 0.23$ in 20% acetone in hexanes.

Step D

- 5 Toluene-4-sulfonic acid 1-{[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propyl ester

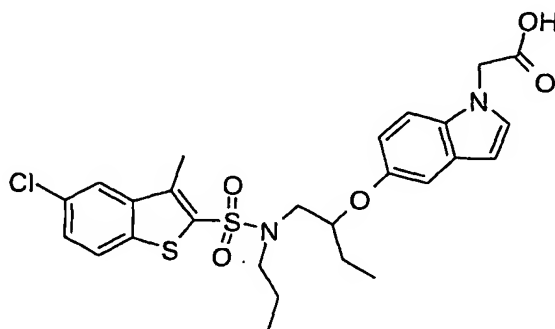


- A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-propyl-amide (1.05 g, 2.79 mmol) and pyridine (0.90 mL, 11.2 mmol) in dichloromethane (140 mL) was treated with dimethylaminopyridine (0.136 g, 1.12 mmol) and p-toluenesulphonic anhydride (1.82 g, 5.59 mmol). The resultant mixture was stirred at ambient temperature for 48h, then diluted with dichloromethane and washed with 1N HCl. The organic layers were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The crude material was purified by flash chromatography, using 20% acetone in hexanes as eluent, to provide 1.29 g (87%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, 2H, $J = 8.3$ Hz), 7.74 (d, 2H, $J = 8.6$ Hz), 7.46 (d, 1H, $J = 8.3$ Hz, 1.8 Hz), 7.33 (d, 2H, $J = 7.7$ Hz), 4.66-4.60 (m, 1H), 3.48 (q, 2H, $J = 5.4$ Hz), 3.18, 3.14 (ABq, 2H, $J = 8.4$ Hz), 2.66 (s, 3H), 2.44 (s, 3H), 1.85-1.78 (m, 1H), 1.69-1.62 (m, 1H), 1.51, 1.48 (ABq, 2H, $J = 7.4$ Hz), 0.88 (t, 3H, $J = 6.8$ Hz), 0.79 (td, 3H, $J = 7.7$ Hz, 4.5 Hz). $R_f = 0.60$ in 50% acetone in hexanes.

-79-

Step E

[5-(1-{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-indol-1-yl]-acetic acid

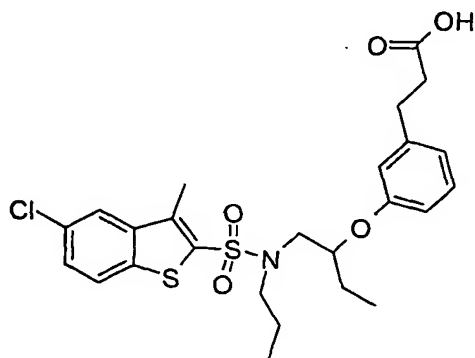


- 5 A solution of (5-hydroxy-indol-1-yl)-acetic acid ethyl ester (0.062 g, 0.28 mmol) and toluene-4-sulfonic acid 1-{[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propyl ester (0.165 g, 0.31 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.138 g, 0.42 mmol), heated to 60 °C under N₂ for 10h. The resulting suspension was cooled to ambient
- 10 temperature, diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude [5-(1-{[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-indol-1-yl]-acetic acid methyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo. The
- 15 residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. MS [EI-] 547 (M-H)⁺.

-80-

Example 2

3-[3-(1-[[[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propoxy)-phenyl]-propionic acid

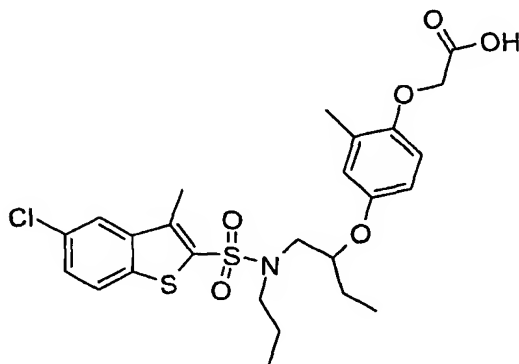


5 A solution of 3-(3-hydroxy-phenyl)-propionic acid methyl ester (0.055 g, 0.31 mmol) and toluene-4-sulfonic acid 1-[[[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propyl ester (0.178 g, 0.34 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.149 g, 0.46 mmol), heated to 60 °C under N₂ for 10h. The resulting suspension was cooled to ambient
10 temperature, diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude 3-[3-(1-[[[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propoxy)-phenyl]-propionic acid methyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo. The
15 residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (dd, 2H, *J* = 5.4 Hz, 3.4 Hz), 7.42 (dd, 1H, *J* = 8.6 Hz, 2.3 Hz), 7.08 (t, 1H, *J* = 7.7 Hz), 6.73 (d, 1H, *J* = 7.7 Hz), 6.60-6.58 (m, 2H), 4.44-4.38 (m, 1H), 3.59 (dd, 1H, *J* = 15.0 Hz, 4.1 Hz), 3.40-3.25 (m, 3H), 2.84 (t, 2H, *J* = 7.3 Hz), 2.64 (t, 2H, *J* = 7.7 Hz), 2.60 (s, 3H), 1.70-1.54 (m, 4H), 0.95 (t, 3H, *J* = 7.7 Hz), 0.83 (t, 3H, *J* = 7.3 Hz). HRMS (ES⁺) *m/z* exact mass calculated for C₂₅H₃₁NO₅S₂Cl 524.1332, found 524.1332.

-81-

Example 3

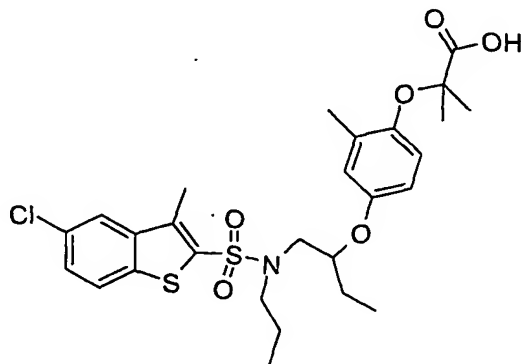
[4-(1-{{(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino}-methyl}-propoxy)-2-methyl-phenoxy]-acetic acid



- 5 A solution of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (0.050 g, 0.26 mmol) and toluene-4-sulfonic acid 1-{{(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino}-methyl}-propyl ester (0.149 g, 0.28 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.125 g, 0.38 mmol), heated to 60 °C under N₂ for 10h. The resulting suspension was cooled to ambient
- 10 temperature, diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude [4-(1-{{(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino}-methyl}-propoxy)-2-methyl-phenoxy]-acetic acid methyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in *vacuo*.
- 15 The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in *vacuo*, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.71-7.69 (m, 2H), 7.42 (dd, 1H, *J* = 7.9 Hz, 2.4 Hz), 6.55-6.47 (m, 3H), 4.58 (s, 2H), 4.32-4.28 (m, 1H), 3.57 (dd, 1H, *J* = 15.1 Hz, 3.6 Hz), 3.41-3.26 (m, 2H), 2.59 (s, 3H), 2.16 (s, 3H), 1.69-1.55 (m, 4H), 0.94 (t, 3H, *J* =
- 20 7.3 Hz), 0.84 (t, 3H, *J* = 7.3 Hz). HRMS (ES⁺) *m/z* exact mass calculated for C₂₅H₃₁NO₆S₂Cl 540.1281, found 540.1284.

Example 4

[4-(1-{{(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino}-methyl}-propoxy)-2-methyl-phenoxy]-acetic acid

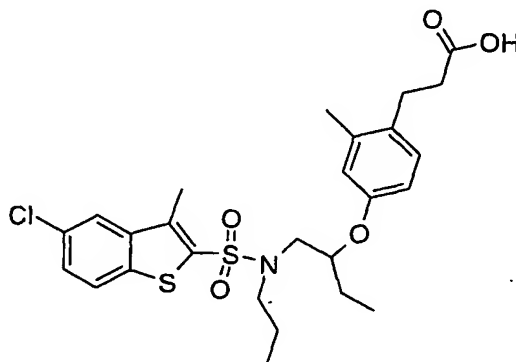


5 A solution of 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (0.051 g, 0.21 mmol) and toluene-4-sulfonic acid 1-{{(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino}-methyl}-propyl ester (0.125 g, 0.24 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.105 g, 0.32 mmol), heated to 60 °C under N₂ for 10h. The resulting suspension was cooled to ambient
10 temperature, diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude 2-[4-(1-{{(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino}-methyl}-propoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated
15 in vacuo. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (m, 2H), 7.44 (dd, 1H, *J* = 8.7 Hz, 2.0 Hz), 6.69 (d, 1H, *J* = 8.7 Hz), 6.54 (dd, 1H, *J* = 3.3 Hz), 6.49 (dd, 1H, *J* = 8.7 Hz, 2.7 Hz), 4.35-4.30 (m, 1H), 3.57 (dd, 1H, *J* = 15.6 Hz, 3.5 Hz), 3.38-3.28 (m, 3H), 2.60 (s, 3H), 2.13 (s, 3H), 1.68-1.56 (m, 4H), 1.54 (s, 6H), 0.95 (t, 3H, *J* = 8.7 Hz), 0.84 (t, 3H, *J* = 6.9 Hz). MS [EI⁺] 568 (M+H)⁺.
20

-83-

Example 5

3-[4-(1-[[[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propoxy)-2-methyl-phenyl]-propionic acid

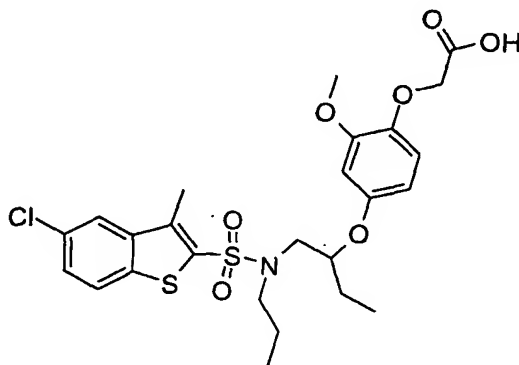


- 5 A solution of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (0.065 g, 0.34 mmol) and toluene-4-sulfonic acid 1-[[[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propyl ester (0.195 g, 0.39 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.164 g, 0.50 mmol), heated to 60 °C under N₂ for 10h. The resulting suspension was cooled to ambient
- 10 temperature, diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude 3-[4-(1-[[[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propoxy)-2-methyl-phenyl]-propionic acid methyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo.
- 15 The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 2H, *J* = 9.2 Hz), 7.42 (dd, 1H, *J* = 8.5 Hz, 2.1 Hz), 6.90 (d, 1H, *J* = 8.5 Hz), 6.49 (d, 2H, *J* = 9.2 Hz), 4.38-4.32 (m, 1H), 3.59 (dd, 1H, *J* = 15.2 Hz, 3.2 Hz), 3.42-3.29 (m, 3H), 2.84 (t, 2H, *J* = 8.3 Hz), 2.59 (t, 2H, *J* = 8.3 Hz), 2.58 (s, 3H), 2.18 (s, 3H), 1.68-1.58 (m, 4H), 0.94 (t, 3H, *J* = 7.6 Hz), 0.85 (t, 3H, *J* = 7.6 Hz). HRMS (ES⁺) *m/z* exact mass calculated for C₂₆H₃₃NO₅S₂Cl 538.1489, found 538.1465.
- 20

-84-

Example 6

[4-(1-[[[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propoxy)-2-methoxy-phenoxy]-acetic acid

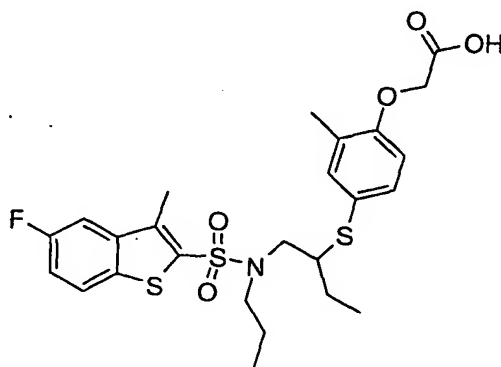


5 A solution of (4-hydroxy-2-methoxy-phenoxy)-acetic acid ethyl ester (0.055 g, 0.24 mmol) and toluene-4-sulfonic acid 1-[[[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propyl ester (0.142 g, 0.27 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.213 g, 0.37 mmol), heated to 60 °C under N₂ for 10h. The resulting suspension was cooled to ambient
10 temperature, diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude [4-(1-[[[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propoxy)-2-methoxy-phenoxy]-acetic acid ethyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in *vacuo*.
15 The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in *vacuo*, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 2H, *J* = 8.0 Hz), 7.43 (dd, 1H, *J* = 8.7 Hz, 2.0 Hz), 6.91 (d, 1H, *J* = 8.0 Hz), 6.34 (d, 1H, *J* = 2.0 Hz), 6.26 (dd, 1H, *J* = 8.7 Hz, 2.0 Hz), 4.42-4.37 (m, 1H), 3.72 (s, 3H), 3.56 (dd, 1H, *J* = 15.3 Hz, 4.0 Hz), 2.84 (t, 2H, *J* = 7.3 Hz), 2.62 (t, 2H, *J* = 8.0 Hz), 2.60 (s, 3H), 1.71-1.55 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz), 0.84 (t, 3H, *J* = 8.0 Hz). HRMS (ES⁺) *m/z* exact mass calculated for C₂₆H₃₂NO₆S₂ClNa 576.1257, found 576.1276.
20

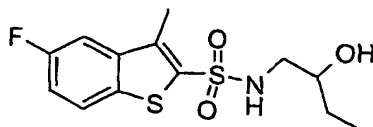
-85-

Example 7

[4-(1-{{(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino}-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid

Step A

5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-amide

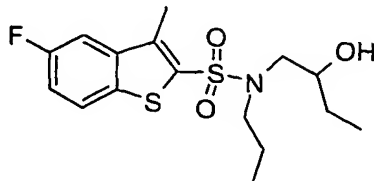


The compound of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (1.0 g, 3.78 mmol) in dichloromethane (10 mL) was added dropwise to a 0 °C solution of 1-amino-2-butanol (0.4 mL, 4.2 mmol) and triethylamine (1.05 mL, 7.55 mmol) in dichloromethane (50 mL). The resulting solution was stirred at ambient temperature for 1h, then diluted with dichloromethane and washed with water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to provide a quantitative yield of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (q, 1H, *J* = 4.5 Hz), 7.46 (dd, 1H, *J* = 9.3 Hz, 2.6 Hz), 7.26 (td, 1H, *J* = 9.3 Hz, 2.6 Hz), 3.70-3.64 (m, 1H), 3.25 (dd, 1H, *J* = 12.7 Hz, 3.3 Hz), 2.92 (dd, 1H, *J* = 12.7 Hz, 8.2 Hz), 2.65 (s, 3H), 1.51-1.43 (m, 2H), 1.04 (t, 3H, *J* = 7.0 Hz), 0.91 (t, 3H, *J* = 7.0 Hz). *R_f* = 0.47 in 50% acetone in hexanes.

-86-

Step B

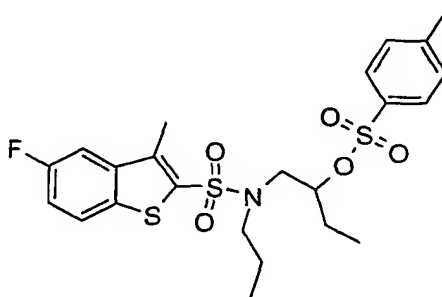
5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-propyl-amide



A solution of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-amide (1.2 g, 3.78 mmol) and 1-iodopropane (0.5 mL, 4.9 mmol) in dimethylformamide (60 mL) was treated with cesium carbonate (1.60 g, 4.9 mmol). The resulting mixture was heated to 50 °C under N₂ for 45 minutes. The reaction mixture was cooled to ambient temperature, and diluted with diethyl ether. The organic layer was washed with 1N HCl and water, dried over Na₂SO₄, and concentrated *in vacuo*. The crude material was purified by flash chromatography, using 20% acetone in hexanes as eluent, to provide 1.3 g (96%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.74 (dd, 1H, *J* = 4.9 Hz, 3.7 Hz), 7.45 (dd, 1H, *J* = 9.2 Hz, 2.4 Hz), 7.23 (td, 1H, *J* = 9.2 Hz, 2.4 Hz), 3.82-3.75 (m, 1H), 3.29, 3.25 (ABq, 2H, *J* = 7.9 Hz), 2.66 (s, 3H), 2.48 (d, 1H, *J* = 3.7 Hz), 1.65-1.56 (m, 2H), 1.55-1.40 (m, 2H), 0.97 (t, 3H, *J* = 7.3 Hz), 0.88 (t, 3H, *J* = 7.3 Hz). MS [EI⁺] 360 (M+H)⁺. R_f = 0.57 in 50% acetone in hexanes.

Step C

Toluene-4-sulfonic acid 1-{[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propyl ester



A solution of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-propyl-amide (0.611 g, 1.7 mmol) and pyridine (0.4 mL, 5.1 mmol) in dichloromethane (85 mL) was treated with dimethylaminopyridine (0.062 g, 0.51 mmol) and *p*-toluenesulphonic anhydride (0.83 g, 2.55 mmol). The resultant mixture was stirred at ambient temperature for 10h, then diluted with dichloromethane and washed with 1N

-87-

HCl. The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo*. The crude material was purified by flash chromatography, using 13% acetone in hexanes as eluent, to provide quantitative yield of the title compound. ^1H NMR (400 MHz, CDCl_3) δ 7.78-7.74 (m, 3H), 7.45 (dd, 1H, $J = 9.2$ Hz, 2.7 Hz), 7.32 (d, 2H, $J = 8.1$ Hz), 7.25 (td, 1H, $J = 9.2$ Hz, 2.7 Hz), 4.66-4.060 (m, 1H), 3.49, 3.47 (ABq, 2H, $J = 6.0$ Hz), 3.21-3.12 (m, 2H), 2.65 (s, 3H), 2.43 (s, 2H), 1.86-1.76 (m, 1H), 1.71-1.60 (m, 1H), 1.54-1.44 (m, 2H), 0.81-0.76 (m, 6H). MS [EI+] 514 (M+H)⁺. $R_f = 0.20$ in 20% acetone in hexanes.

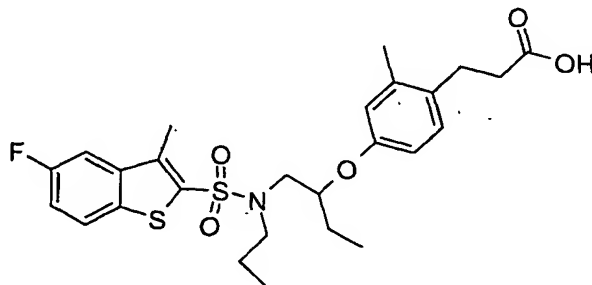
Step D

[4-(1-{[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid

A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.11 g, 0.46 mmol) and toluene-4-sulfonic acid 1-{[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propyl ester (0.12 g, 0.23 mmol) in dimethylformamide (2 mL) was treated with sodium hydride (0.02 g, 0.46 mmol) and stirred at ambient temperature under N_2 . The resulting suspension was diluted with ethyl acetate, and washed with 1N HCl, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. A solution of crude [4-(1-{[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo. The residue was diluted with 1N HCl, extracted with CH_2Cl_2 , dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ^1H NMR (400 MHz, CDCl_3) δ 9.20 (s, 1H), 7.74 (dd, 1H, $J = 4.9$ Hz, 3.6 Hz), 7.42 (dd, 1H, $J = 9.1$ Hz, 2.4 Hz), 7.24-7.18 (m, 3H), 6.61 (d, 1H, $J = 8.5$ Hz), 4.67 (s, 2H), 3.40, 3.26 (ABq, 1H, $J = 9.7$ Hz), 3.37, 3.23 (ABq, 1H, $J = 9.7$ Hz), 3.21-3.06 (m, 2H), 2.56 (s, 3H), 2.22 (s, 3H), 1.94-1.87 (m, 1H), 1.50-1.36 (m, 3H), 1.08 (t, 3H, $J = 7.3$ Hz), 0.8 (t, 3H, $J = 7.3$ Hz). HRMS (ES+) m/z exact mass calculated for $\text{C}_{25}\text{H}_{31}\text{NO}_5\text{FS}_3$ 540.1348, found 540.1358.

Example 8

3-[4-(1-{{(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-2-methyl-phenyl]-propionic acid



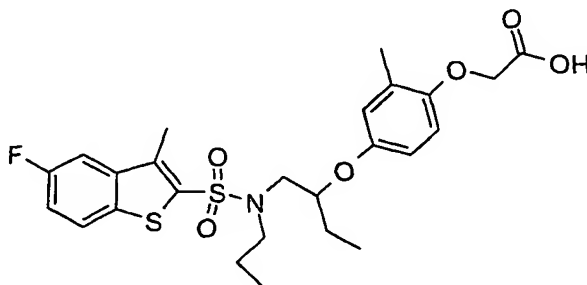
5 A solution of 3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester (0.042 g, 0.22 mmol) and Toluene-4-sulfonic acid 1-{{(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propyl ester (0.122 g, 0.24 mmol) in acetonitrile (2 mL) was treated with cesium carbonate (0.23 g, 0.70 mmol), heated to 65 °C under N₂ for 18h. The resulting suspension was cooled to ambient temperature, 10 diluted with ethyl acetate, and washed with 1N HCl, water, and brine. The organic layer was dried over Na₂SO₄, concentrated *in vacuo*, and purified by flash chromatography, using 20% acetone in hexanes as eluent. R_f=0.14 in 20 % acetone in hexanes. A solution of semicrude 3-[4-(1-{{(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propoxy)-2-methyl-phenyl]-propionic acid methyl ester and 5N NaOH 15 (0.5 mL) in ethanol (4 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated *in vacuo*. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated *in vacuo*, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (dd, 1H, *J* = 4.5 Hz), 7.38 (dd, 1H, *J* = 9.8 Hz, 2.3 Hz), 7.22 (dd, 1H, *J* = 9.0 Hz, 3.0 Hz), 6.92 (d, 1H, *J* = 8.3 Hz), 6.53-6.51 (m, 2H). 3.59 (dd, 1H, *J* = 15.0 Hz, 3.8 Hz), 3.41-3.26 (m, 3H), 2.84 (t, 2H, *J* = 7.5 Hz), 2.59 (t, 2H, *J* = 7.5 Hz), 2.58 (s, 3H), 2.19 (s, 3H), 1.69-1.58 (m, 4H), 0.95 (t, 3H, *J* = 7.5 Hz), 0.85 (t, 3H, *J* = 7.5 Hz). MS [EI⁺] 522 (M+H)⁺.

20

-89-

Example 9

[4-(1-[[[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propoxy)-2-methyl-phenoxy]-acetic acid

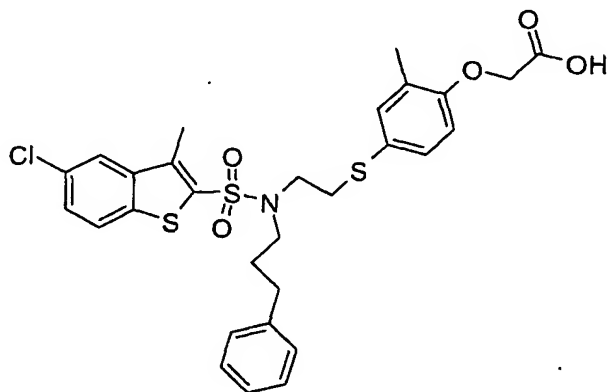


- 5 A solution of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (0.05 g, 0.31 mmol) and toluene-4-sulfonic acid 1-[[[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propyl ester (0.173 g, 0.34 mmol) in dimethylformamide (2 mL) was treated with cesium carbonate (0.166 g, 0.51 mmol), heated to 60 °C under N₂ for 10h. The resulting suspension was cooled to ambient
- 10 temperature, diluted with ethyl acetate, and washed with 1N HCl, water, and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude [4-(1-[[[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propoxy)-2-methyl-phenoxy]-acetic acid methyl ester and 5N NaOH (0.5 mL) in ethanol (4 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and
- 15 concentrated in vacuo. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H), 7.73 (dd, 1H, *J* = 8.6 Hz, 4.9 Hz), 7.39 (dd, 1H, *J* = 9.8 Hz, 2.4 Hz), 7.23 (td, 1H, *J* = 9.8 Hz, 2.4 Hz), 6.57-6.49 (m, 3H), 4.59 (s, 2H), 4.34-4.29 (m, 1H), 3.57 (dd, 1H, *J* = 15.3 Hz, 3.7 Hz), 3.39-3.28 (m, 3H), 2.59 (s, 3H), 2.16 (s, 3H), 1.69-1.50 (m, 4H), 0.94 (t, 3H, *J* = 7.3 Hz), 0.84 (t, 3H, *J* = 7.3 Hz). HRMS (ES⁺) *m/z* exact mass calculated for C₂₅H₃₁NO₆FS₂ 524.1577. found 524.1569.
- 20

-90-

Example 10

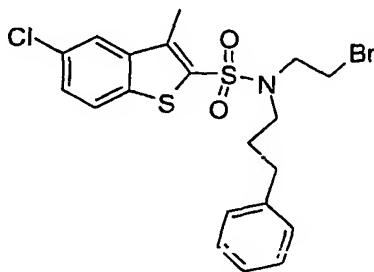
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3-phenyl-propyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-ethyl)-(3-phenyl-propyl)-amide



A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-ethyl)-(3-phenyl-propyl)-amide (0.196 g, 0.46 mmol) and carbon tetrabromide (0.23 g, 0.69 mmol) in dichloromethane (5 mL) was treated with triphenylphosphine (0.18 g, 0.69 mmol). The resulting mixture was stirred at ambient temperature until all 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-ethyl)-(3-phenyl-propyl)-amide was consumed, then adsorbed onto silica gel. The crude material was purified by flash chromatography, using 9% acetone in hexanes as eluent, to provide 0.151 g (67%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, 1H, *J* = 2.1 Hz), 7.74 (d, 1H, *J* = 9.0 Hz), 7.46 (dd, 1H, *J* = 9.0 Hz, 2.1 Hz), 7.26 (t, 2H, *J* = 7.4 Hz), 7.20 (t, 1H, *J* = 7.4 Hz), 7.11 (d, 2H, *J* = 8.2 Hz), 3.62-3.58 (m, 2H), 3.49-3.45 (m, 2H), 3.30 (t, 2H, *J* = 7.4 Hz), 2.63 (t, 2H, *J* = 7.4 Hz), 2.62 (s, 3H), 1.92 (p, 2H, *J* = 7.4 Hz).

-91-

Step B

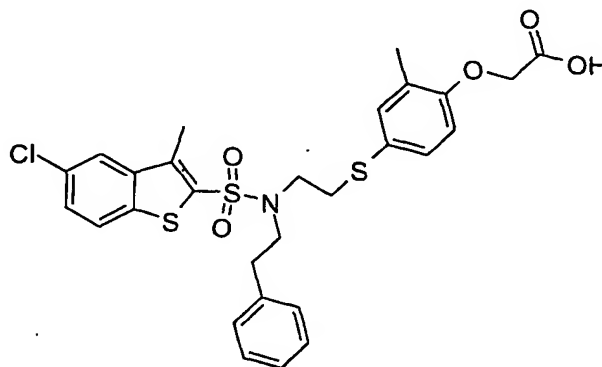
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3-phenyl-propyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester

- 5 (0.066 g, 0.29 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-ethyl)-(3-phenyl-propyl)-amide (0.15 g, 0.32 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.143 g, 0.44 mmol) and heated at 60 °C under N₂ for 10h. The resulting suspension was diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A
- 10 solution of crude (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3-phenyl-propyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS
- 15 to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, 1H, *J* = 2.0 Hz), 7.71 (d, 1H, *J* = 9.2 Hz), 7.44 (dd, 1H, *J* = 9.2 Hz, 2.0 Hz), 7.27-7.24 (m, 2H), 7.20-7.08 (m, 5H), 6.62 (d, 1H, *J* = 8.5 Hz), 4.66 (s, 2H), 3.34 (t, 2H, *J* = 7.8 Hz), 3.26 (t, 2H, *J* = 7.8 Hz), 3.00 (t, 2H, *J* = 7.8 Hz), 2.59 (t, 2H, *J* = 7.8 Hz), 2.52 (s, 3H), 2.23 (s, 3H), 1.83 (p, 2H, *J* = 7.8 Hz). HRMS (ES⁺) *m/z* exact mass calculated for C₂₉H₃₀NO₅NaS₃Cl
- 20 626.0872, found 626.0866.

Example 11

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

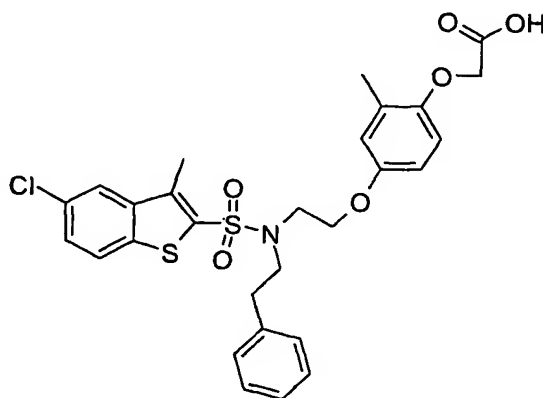


5 A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.061 g, 0.27 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-ethyl)-phenethyl-amide (0.14 g, 0.30 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.132 g, 0.40 mmol) and heated at 60 °C under N₂ for 10h. The resulting suspension was diluted with diethyl ether, and washed with 1N HCl and
10 water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*.

A solution of crude (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo. The residue was diluted with 1N HCl,
15 extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, 1H, *J* = 2.2 Hz), 7.71 (d, 1H, *J* = 8.3 Hz), 7.44 (dd, 1H, *J* = 8.9 Hz, 1.7 Hz), 7.23-7.16 (m, 1H), 7.07 (d, 2H, *J* = 7.2 Hz), 6.65 (d, 1H, *J* = 8.9 Hz), 4.68 (s, 2H), 3.47 (t, 2H, *J* = 7.7 Hz), 3.37 (t, 2H, *J* = 7.7 Hz), 2.95 (t, 2H, *J* = 7.7 Hz), 2.82 (t, 2H, *J* =
20 7.7 Hz), 2.52 (s, 3H), 2.26 (s, 3H). MS [EI⁺] 590 (M+H)⁺.

Example 12

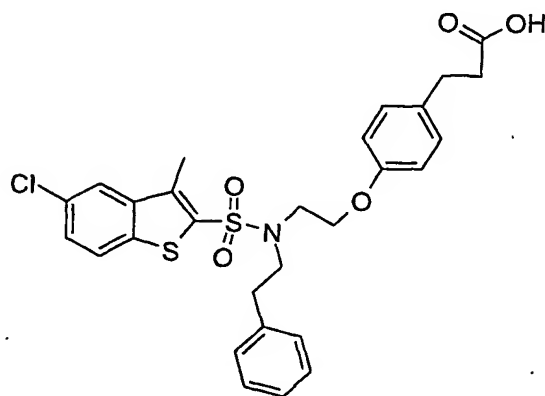
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethoxy}-2-methyl-phenoxy)-acetic acid



A solution of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (0.052 g, 0.27 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-ethyl)-phenethyl-amide (0.14 g, 0.29 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.132 g, 0.40 mmol) and heated at 60 °C under N₂ for 10h. The resulting suspension was diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethoxy}-2-methyl-phenoxy)-acetic acid methyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated *in vacuo*. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated *in vacuo*, and purified by LCMS to provide the title compound. HRMS (ES⁺) *m/z* exact mass calculated for C₂₈H₂₉NO₆S₂Cl 574.1125, found 574.1122.

Example 13

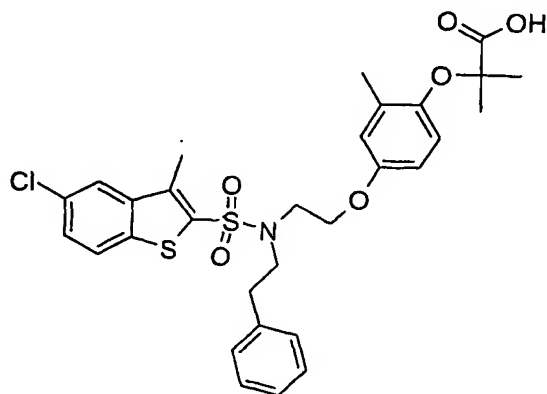
3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethoxy}-phenyl)-propionic acid



- 5 A solution of 3-(4-hydroxy-phenyl)-propionic acid methyl ester (0.064 g, 0.36 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-ethyl)-phenethyl-amide (0.19 g, 0.39 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.174 g, 0.53 mmol) and heated at 60 °C under N₂ for 10h. The resulting suspension was diluted with diethyl ether, and washed with 1N HCl and water.
- 10 The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude 3-(4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethoxy}-phenyl)-propionic acid methyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian
- 15 ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, 2H, *J* = 8.6 Hz), 7.44 (dd, 1H, *J* = 8.6 Hz, 2.0 Hz), 7.26-7.13 (m, 7H), 6.78 (d, 1H, *J* = 7.3 Hz), 6.63 (dd, 1H, *J* = 8.6 Hz, 2.0 Hz), 6.63 (dd, 1H, *J* = 8.6 Hz, 2.0 Hz), 6.58 (s, 1H), 4.08 (t, 2H, *J* = 5.3 Hz), 3.71 (t, 2H, *J* = 5.3 Hz), 3.63 (t, 2H, *J* = 8.0 Hz), 2.99 (t, 2H, *J* = 8.0 Hz), 2.87 (t, 2H, *J* = 8.0 Hz), 2.64 (t, 2H, *J* = 8.0 Hz), 2.62 (s, 3H). HRMS (ES⁺) *m/z* exact mass calculated for C₂₈H₂₈NO₅NaS₂Cl 580.0995, found 580.1000.
- 20

Example 14

2-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

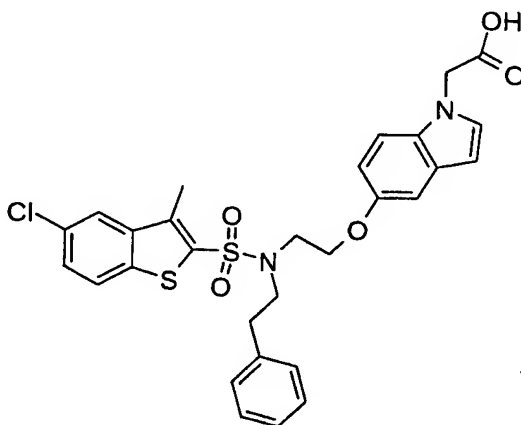


A solution of 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (0.062 g, 0.26 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-ethyl)-phenethyl-amide (0.14 g, 0.29 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.127 g, 0.39 mmol) and heated at 60 °C under N₂ for 10h. The resulting suspension was diluted with diethyl ether, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*.

A solution of crude 2-(4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethoxy}-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated *in vacuo*. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated *in vacuo*, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.76-7.70 (m, 2H), 7.45 (dd, 2H, *J* = 8.2 Hz, 2.1 Hz), 7.25-7.14 (m, 4H), 7.06 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 6.76 (d, 1H, *J* = 8.2 Hz), 6.58-6.51 (m, 1H), 4.05 (t, 2H, *J* = 6.2 Hz), 3.68 (t, 2H, *J* = 6.2 Hz), 3.62 (t, 2H, *J* = 8.2 Hz), 2.98 (t, 2H, *J* = 8.2 Hz), 2.62 (s, 3H), 2.19 (s, 3H), 1.55 (s, 6H). HRMS (ES⁺) *m/z* exact mass calculated for C₃₀H₃₃NO₆S₂Cl 602.1438, found 602.1422.

Example 15

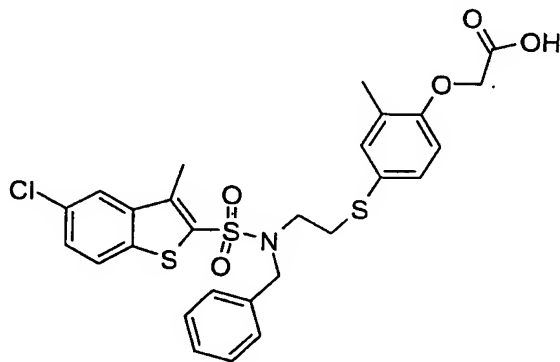
(5-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethoxy}-indol-1-yl)-acetic acid



- 5 A solution of (5-hydroxy-indol-1-yl)-acetic acid ethyl ester (0.066 g, 0.30 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-ethyl)-phenethyl-amide (0.16 g, 0.33 mmol) in dimethylformamide (5 mL) was treated with cesium carbonate (0.147 g, 0.45 mmol) and heated at 60 °C under N₂ for 10h. The resulting suspension was diluted with diethyl ether, and washed with 1N HCl and water.
- 10 The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude (5-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-phenethyl-amino]-ethoxy}-indol-1-yl)-acetic acid ethyl ester and 5N NaOH (1 mL) in ethanol (5 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated *in vacuo*. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian
- 15 ChemElut cartridge, concentrated *in vacuo*, and purified by LCMS to provide the title compound. HRMS (ES⁺) *m/z* exact mass calcd. for C₂₉H₂₇N₂O₅NaS₂Cl 605.0948, found 605.0956.

Example 16

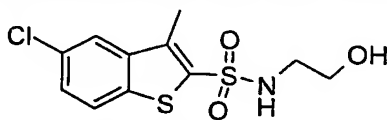
(4-{2-[Benzyl-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-ethyl)-amide

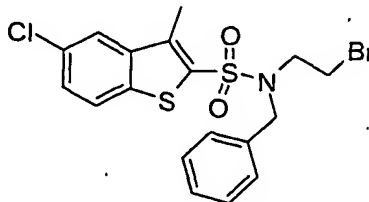


5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (2.02 g, 7.18 mmol) was added portion wise to a 0 °C solution of ethanolamine (0.5 mL, 7.90 mmol) and triethylamine (2.0 mL, 14.4 mmol) in dichloromethane (100 mL). The resulting solution was stirred at ambient temperature for 2h, then diluted with dichloromethane and washed with water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by flash chromatography to provide 1.8 g (80%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.15 (t, 1H, *J* = 5.9 Hz), 8.08 (d, 1H, *J* = 8.8 Hz), 8.02 (d, 1H, *J* = 2.3 Hz), 7.56 (dd, 1H, *J* = 8.8 Hz, 2.3 Hz), 4.49 (s, 2H), 3.56 (t, 2H, *J* = 8.2 Hz), 3.18 (t, 2H, *J* = 7.8 Hz), 2.70 (s, 3H). *R_f* = 0.35 in 50% acetone in hexanes.

-98-

Step B

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid benzyl-(2-bromo-ethyl)-amide



A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-ethyl)-amide (1.0 g, 3.27 mmol) and benzyl bromide (0.51 mL, 4.25 mmol) in dimethylformamide (60 mL) was treated with cesium carbonate (1.39 g, 4.25 mmol). The resulting mixture was heated to 50 °C under N₂ for 2h. The reaction mixture was cooled to ambient temperature, and diluted with diethyl ether. The organic layer was washed with 1N HCl and water, dried over Na₂SO₄, and concentrated *in vacuo*. The crude material was purified by flash chromatography, using 20% acetone in hexanes as eluent. R_f = 0.52 in 50% acetone in hexanes.

A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid benzyl-(2-hydroxy-ethyl)-amide and carbon tetrabromide (1.63 g, 4.91 mmol) in dichloromethane (20 mL) was treated with triphenylphosphine (1.29 g, 4.91 mmol). The resulting mixture was stirred at ambient temperature for 10h, then adsorbed onto silica gel. The crude material was purified by flash chromatography, using 10% acetone in hexanes as eluent, to provide 1.10 g (73%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, 1H, J = 2.2 Hz), 7.77 (d, 1H, J = 8.6 Hz), 7.48 (dd, 1H, J = 8.6 Hz, 2.2 Hz), 7.34-7.27 (m, 5H), 4.49 (s, 2H), 3.56 (t, 2H, J = 8.2 Hz), 3.18 (t, 2H, J = 8.2 Hz), 2.70 (s, 3H). R_f = 0.66 in 50% acetone in hexanes.

Step C

(4-{2-[Benzyl]-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-amino}-ethylsulfanyl)-2-methyl-phenoxy)-acetic acid

A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.30 g, 0.13 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid benzyl-(2-bromo-ethyl)-amide (0.05 g, 0.10 mmol) in dimethylformamide (2 mL) was treated with sodium hydride (0.01 g, 0.13 mmol) and stirred at ambient temperature under N₂. The

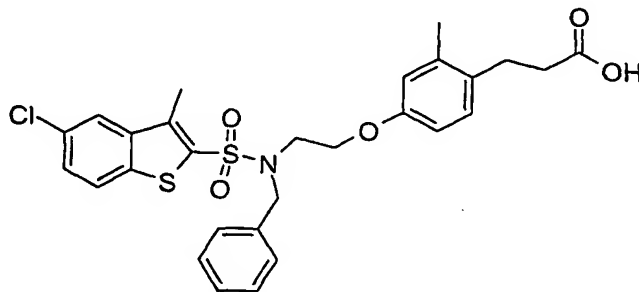
-99-

resulting suspension was diluted with ethyl acetate, and washed with 1N HCl, water, and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*.

A solution of crude [4-(1-{{(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester and 5N NaOH (1 mL) in ethanol (4 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, 1H, *J* = 1.9 Hz), 7.73 (d, 1H, *J* = 8.4 Hz), 7.45 (dd, 1H, *J* = 8.4 Hz, 1.9 Hz), 7.28-7.19 (m, 5H), 7.02 (s, 1H), 6.95 (d, 1H, *J* = 8.4 Hz), 6.54 (d, 1H, *J* = 8.4 Hz), 4.65 (s, 2H), 4.40 (s, 2H), 3.29 (t, 2H, *J* = 8.8 Hz), 2.73 (t, 2H, *J* = 8.8 Hz), 2.57 (s, 3H), 2.19 (s, 3H). HRMS (ES⁺) *m/z* exact mass calculated for C₂₇H₂₇NO₅S₃Cl 576.0740, found 576.0751.

Example 17

3-(4-{2-[Benzyl-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-amino]-ethoxy}-2-methyl-phenyl)-propionic acid



A solution of 3-(4-hydroxy-phenyl)-propionic acid methyl ester (0.056 g, 0.29 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid benzyl-(2-bromoethyl)-amide (0.145 g, 0.32 mmol) in dimethylformamide (2 mL) was treated with cesium carbonate (0.141 g, 0.43 mmol) and heated at 60 °C under N₂ for 10h. The resulting suspension was diluted with ethyl acetate, and washed with 1N HCl and water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude 3-(4-{2-[benzyl-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-amino]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester and 5N NaOH (1 mL) in ethanol (4 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo.

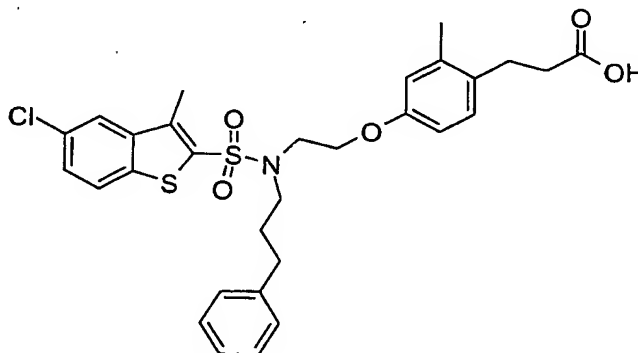
-100-

The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.71-7.70 (m, 2H), 7.48 (td, 1H, *J* = 6.3 Hz, 2.3 Hz), 7.31-7.19 (m, 5H), 6.91 (d, 1H, *J* = 8.6 Hz), 6.37 (d, 1H, *J* = 8.6 Hz), 6.30 (d, 1H, *J* = 2.3 Hz), 4.63 (s, 2H), 4.28 (d, 1H, *J* = 6.3 Hz), 3.90 (t, 2H, *J* = 5.8 Hz), 3.60 (t, 2H, *J* = 5.8 Hz), 2.82 (t, 2H, *J* = 8.1 Hz), 2.64 (s, 3H), 2.58 (t, 2H, *J* = 8.1 Hz), 2.16 (s, 3H). HRMS (ES+) *m/z* exact mass calculated for C₂₈H₂₈NO₅NaS₂Cl 580.0995, found 580.0989.

10

Example 18

3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3-phenyl-propyl)-amino]-ethoxy}-2-methyl-phenyl)-propionic acid



A solution of 3-(4-hydroxy-phenyl)-propionic acid methyl ester (0.054 g, 0.28 mmol) and 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-ethyl)-(3-phenyl-propyl)-amide (0.149 g, 0.31 mmol) in dimethylformamide (2 mL) was treated with cesium carbonate (0.149 g, 0.46 mmol) and heated at 60 °C under N₂ for 10h. The resulting suspension was diluted with ethyl acetate, and washed with 1N HCl, water, and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude 3-(4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3-phenyl-propyl)-amino]-ethoxy}-2-methyl-phenyl)-propionic acid ethyl ester and 5N NaOH (1 mL) in ethanol (4 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated in vacuo. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.78-7.70 (m, 2H), 7.45 (dd, 2H, *J* = 8.1 Hz, 1.8 Hz), 7.25-6.97 (m, 5H), 6.51 (dd, 1H, *J* = 8.1 Hz, 1.8 Hz), 6.48

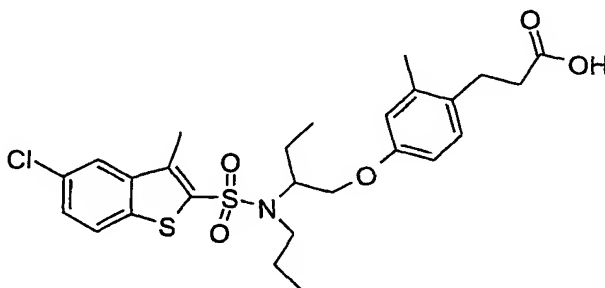
-101-

(s, 1H), 4.07 (t, 2H, $J = 6.1$ Hz), 3.64 (t, 2H, $J = 6.1$ Hz), 3.41 (t, 2H, $J = 7.3$ Hz), 2.86 (t, 2H, $J = 7.3$ Hz), 2.66-2.53 (m, 5H), 2.21 (s, 3H), 2.03-1.95 (m, 3H), 1.84 (p, 1H, $J = 7.3$ Hz). HRMS (ES+) m/z exact mass calculated for $C_{30}H_{32}NO_5NaS_2Cl$ 608.1308, found 608.1312.

5

Example 19

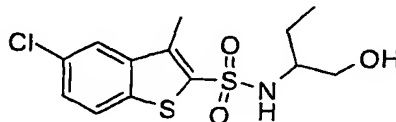
3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-butoxy}-2-methyl-phenyl)-propionic acid



10

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-hydroxymethyl-propyl)-amide



5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (1.08 g, 3.84

mmol) was added portion-wise to a 0 °C solution of 2-amino-1-butanol (0.4 mL, 4.22

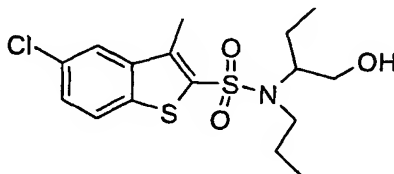
15 mmol) and triethylamine (1.1 mL, 7.68 mmol) in dichloromethane (50 mL). The resulting solution was stirred at ambient temperature for 2h, then diluted with chloroform and washed with water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to provide 1.25 g (98%) of the title compound. 1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 1H, $J = 2.0$ Hz), 7.71 (d, 1H, $J = 8.2$ Hz), 7.41 (dd, 1H, $J = 8.2$ Hz, 2.0 Hz), 3.53 (qd, 2H, $J = 10.0$ Hz, 4.0 Hz), 3.34-3.30 (m, 1H), 2.64 (s, 3H), 1.58-1.44 (m, 2H), 0.99 (t, 3H, $J = 6.9$ Hz). $R_f = 0.41$ in 50% acetone in hexanes.

20

-102-

Step B

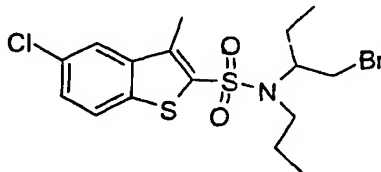
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-hydroxymethyl-propyl)-propyl-amide



A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-hydroxymethyl-propyl)-amide (1.25 g, 3.74 mmol) and 1-iodopropane (0.47 mL, 4.87 mmol) in dimethylformamide (60 mL) was treated with cesium carbonate (1.59 g, 4.87 mmol). The resulting mixture was heated to 50 °C under N₂ until all of the 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-hydroxymethyl-propyl)-amide was consumed. The reaction mixture was cooled to ambient temperature, and diluted with diethyl ether. The organic layer was washed with 1N HCl, water, and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to provide quantitative yield of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (s, 1H), 7.71 (d, 1H, *J* = 1.7 Hz), 7.68 (d, 1H, *J* = 8.4 Hz), 7.38 (dd, 1H, *J* = 8.4 Hz, 1.7 Hz), 3.78-3.71 (m, 1H), 3.57 (td, 2H, *J* = 10.4 Hz, 5.9 Hz), 3.29 (m, 1H), 3.13-3.045 (m, 1H), 2.63 (s, 3H), 1.71-1.61 (m, 2H), 1.58-1.46 (m, 1H), 1.41-1.30 (m, 1H), 0.85 (t, 3H, *J* = 7.4 Hz), 0.70 (t, 3H, *J* = 7.4 Hz). MS [EI⁺] 376 (M+H)⁺. R_f = 0.63 in 50% acetone in hexanes.

Step C

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-bromomethyl-propyl)-propyl-amide



A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-hydroxymethyl-propyl)-propyl-amide and carbon tetrabromide (1.86 g, 5.61 mmol) in dichloromethane (25 mL) was treated with triphenylphosphine (1.47 g, 5.61 mmol). The resulting mixture was stirred at ambient temperature until 5-chloro-3-methyl-

-103-

benzo[b]thiophene-2-sulfonic acid (1-hydroxymethyl-propyl)-propyl-amide was consumed, then adsorbed onto silica gel. The crude material was purified by flash chromatography, using 10% acetone in hexanes as eluent, to provide 0.86 g (52% over two steps) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.75 (t, 1H, *J* = 2.7 Hz), 7.74 (dd, 1H, *J* = 8.4 Hz, 3.4 Hz), 7.42 (dt, 1H, *J* = 8.4 Hz, 3.4 Hz), 4.11 (t, 1H, *J* = 8.1 Hz), 3.92 (t, 1H, *J* = 8.1 Hz), 3.41-3.23 (m, 1H), 3.24-3.11 (m, 2H), 2.68 (s, 3H), 1.75-1.61 (m, 2H), 1.59-1.46 (m, 2H), 0.91-0.79 (m, 6H). *R*_f = 0.70 in 50% acetone in hexanes.

Step D

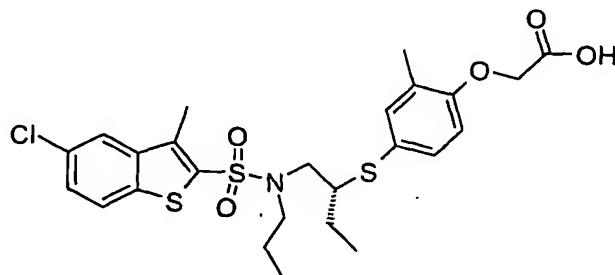
3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-butoxy}-2-methyl-phenyl)-propionic acid

A solution of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (0.060 g, 0.31 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-bromomethyl-propyl)-propyl-amide (0.149 g, 0.34 mmol) in dimethylformamide (2 mL) was treated with cesium carbonate (0.151 g, 0.46 mmol) and heated at 50 °C under N₂ for 10h. The resulting suspension was diluted with ethyl acetate, and washed with 1N HCl, water, and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. A solution of crude 3-(4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-butoxy}-2-methyl-phenyl)-propionic acid ethyl ester and 5N NaOH (1 mL) in ethanol (4 mL) was refluxed under nitrogen for 1h, cooled to ambient temperature, and concentrated *in vacuo*. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried through a Varian ChemElut cartridge, concentrated *in vacuo*, and purified by LCMS to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, 1H, *J* = 1.4 Hz), 7.71 (d, 1H, *J* = 4.5 Hz), 7.43 (dd, 1H, *J* = 8.8 Hz, 2.1 Hz), 6.91 (d, 1H, *J* = 8.8 Hz), 6.38 (dd, 1H, *J* = 8.2 Hz, 2.5 Hz), 6.16 (d, 1H, *J* = 2.5 Hz), 4.08 (p, 1H, *J* = 5.6 Hz), 3.95-3.86 (m, 2H), 3.45-3.19 (m, 2H), 2.82 (t, 2H, *J* = 7.4 Hz), 2.65 (s, 3H), 2.55 (t, 2H, *J* = 7.4 Hz), 2.11 (s, 3H), 1.82-1.60 (m, 4H), 0.94 (t, 3H, *J* = 7.4 Hz), 0.89 (t, 3H, *J* = 7.4 Hz). HRMS (ES⁺) *m/z* exact mass calculated for C₂₆H₃₃NO₅S₂Cl 538.1489, found 538.1477.

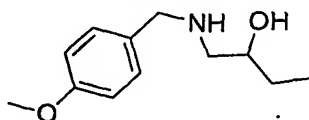
-104-

Example 20

[4-(1-{{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid

Step A

1-(4-Methoxy-benzylamino)-butan-2-ol

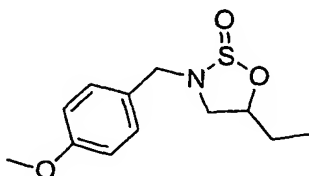


1-amino-2-butanol (15.0 mL, 0.157mol) was added to a 0 °C suspension of *p*-anisaldehyde (21.0 mL, 0.172mol) and sodium sulphate (26.68 g, 0.188mol) in dry CH₂Cl₂ (150 mL). The resulting mixture was stirred at room temperature for one hour, filtered, and concentrated *in vacuo*. The residue was diluted with 4°A molecular sieve-dried ethanol (100 mL) and cooled to 0 °C. Sodium borohydride (5.92 g, 0.157mol) was added to the solution in two portions and the resulting mixture was stirred at room temperature for two hours. The resultant mixture was concentrated *in vacuo*, then partitioned between CH₂Cl₂ and 1 N NaOH. The organic layer was acidified to pH 10 with 1N HCl, dried over sodium sulphate, and concentrated *in vacuo* to give >99% yield of 1-(4-methoxy-benzylamino)-butan-2-ol. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 3.78s, 3H), 3.72. 3.68 (ABq, 2H, *J* = 12.4 Hz) 3.56 - 3.50 (m, 1H), 2.71 (dd, 1H, *J* = 12.3 Hz, 2.8 Hz), 2.49 (dd, 1H, *J* = 12.3 Hz, 9.6 Hz), 1.46-1.38 (m, 2H), 0.92t, 3H, *J* = 7.4 Hz). MS [EI+] 210 (M+H)⁺.

-105-

Step B

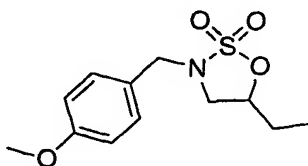
5-Ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2-oxide



5 Thionyl chloride (21.1 mL, 0.29mol) was added dropwise to a -78 °C solution of 1-(4-Methoxy-benzylamino)-butan-2-ol (32.75 g, 0.16mol) and triethylamine (81.8 mL, 0.59mol) in dry CH₂Cl₂. The resulting mixture was stirred at -78 °C for 40 minutes, then warmed to 0 °C for five hours. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The organic layers were combined, dried over sodium sulphate, and concentrated *in vacuo*. The residue was purified by flash chromatography, using 11% acetone in hexanes as eluent, and gave 15.35 g (39%) of 5-ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2-oxide. ¹H NMR (400 MHz, CDCl₃) δ 7.28 (dd, 2H, *J* = 8.5 Hz, 4.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 5.02-4.96 (m, 1H), 4.54-4.47 (m, 1H), 4.24, 4.22 (ABq, 2H, *J* = 5.9 Hz isomer 1), 3.91, 3.79 (ABq, 2H, *J* = 13.3 Hz isomer 2), 3.79, s, 3H), 3.41, 3.39 (ABq, 1H, *J* = 6.1 Hz isomer 1) 3.29, 3.27 (ABq, 1H, *J* = 6.1 Hz isomer 2) 3.12, 3.10 (ABq, 1H, *J* = 9.6 Hz isomer 1) 2.92, 2.90 (ABq, 1H, *J* = 9.6 Hz isomer 2) 1.98-1.77 (m, 2H isomer 1), 1.76-1.57 (m, 2H isomer 2), 1.00t, 3H, *J* = 7.5 Hz, 0.94t, 3H, *J* = 7.5 Hz. *R*_f=0.31 in 33% acetone in hexanes.

Step C

5-Ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2,2-dioxide



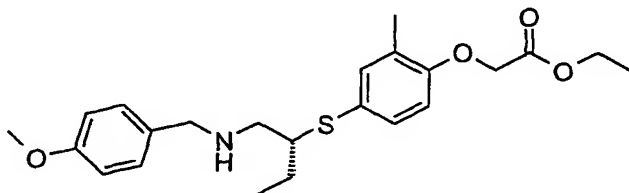
25 Ruthenium (III) chloride (0.27 g, 1.32 mmol) was added to a biphasic solution of 5-ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2-oxide (15.35 g, 60.1 mmol), sodium periodate (25.7 g, 0.12mol), CCl₄ (150 mL), CH₃CN (150 mL), and water (180 mL). The resulting mixture was stirred at room temperature for three hours, and then filtered through a pad of celite. The filtrate was diluted with CH₂Cl₂ and washed

-106-

with sodium thiosulphate solution and water. The residue was purified by flash chromatography, using 11% acetone in hexanes as eluent, and gave 14.33 g (88 %) of 5-ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2,2-dioxide. This material was resolved using chiral HPLC (Chiralpak OJ 4.6 x 150 mm, 30/70 alcohol/heptane, 0.6 mL/min, 240 nm UV setting) to give enantiomers: isomer 1, (>98% ee, *R*) and isomer 2, (>98% ee *S*). ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 4.69-4.62 (m, 1H), 4.23, 4.03 (ABq, 2H, *J* = 13.4 Hz), 3.80s, 3H), 3.35 (dd, 1H, *J* = 9.5 Hz, 6.2 Hz) 3.03 (dd, 1H, *J* = 9.5 Hz, 8.2 Hz) 1.92-1.81 (m, 1H), 1.75-1.65 (m, 1H), 0.98t, 3H, *J* = 7.5 Hz). *R*_f = 0.31 in 33% acetone in hexanes.

Step D

(4-{1-[(4-Methoxy-benzylamino)-methyl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester

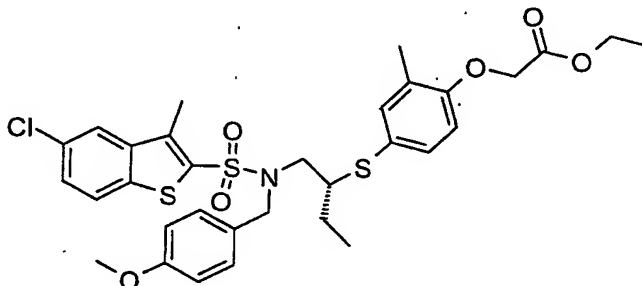


A 0 °C solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (6.66 g, 29.43 mmol) in dimethylformamide (10 mL) was treated with sodium hydride (1.18 g, 29.43 mmol). The suspension was flushed with N₂ while stirring for 15 minutes at 0 °C. 5-Ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2,2-dioxide (5.32 g, 19.62 mmol) in dimethylformamide (10 mL) was added and the resulting mixture was heated at 50 °C for 4h. The reaction mixture was cooled to ambient temperature, diluted with diethyl ether, and stirred with 1N HCl. After 8h, the mixture was basified to pH7 with saturated aqueous sodium bicarbonate solution. The organic layer was washed with water and brine, dried over sodium sulphate, treated with trifluoroacetic acid (4.4 mL, 58.86 mmol), and concentrated *in vacuo* to provide 15.6 g (84%) of the title compound as a TFA salt. ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, 2H, *J* = 9.1 Hz), 6.95 (d, 1H, *J* = 1.4 Hz), 6.87-6.84 (m, 1H), 6.85 (d, 2H, *J* = 8.7 Hz), 6.43 (d, 1H, *J* = 9.1 Hz), 4.55 (s, 2H), 4.20 (p, 2H, *J* = 7.0 Hz), 4.20-4.06 (m, 2H), 3.74 (s, 3H), 3.09-3.02 (m, 2H), 2.86-2.74 (m, 1H), 2.09 (s, 3H), 1.42 (p, 2H, *J* = 7.0 Hz), 1.22 (t, 3H, *J* = 7.0 Hz), 0.95 (t, 3H, *J* = 7.0 Hz). MS [EI⁺] 418 (M+H)⁺.

-107-

Step E

(4-{1-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-methyl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester

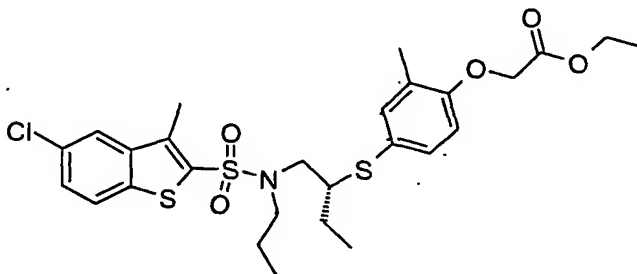


5 A 0°C solution of (4-{1-[(4-methoxy-benzylamino)-methyl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (9.43 g, 18.97 mmol) in dichloromethane (200 mL) was treated with triethylamine (21.2 mL, 151.76 mmol). Sulfonyl chloride (6.93 g, 24.6 mmol) was added all at once as a solid and the reaction mixture was warmed to ambient temperature for 1.5h. The reaction mixture was diluted with dichloromethane and washed with 1N HCl. The organic layers were combined, dried over M gSO₄, and concentrated *in vacuo*. The crude material was purified by flash chromatography, using 11% acetone in hexanes, to provide 4.76 g (45%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, 2H, *J* = 1.7 Hz), 7.75 (d, 2H, *J* = 8.7 Hz), 7.44 (dd, 1H, *J* = 8.7 Hz, 1.7 Hz), 7.22 (dd, 1H, *J* = 8.7 Hz, 2.1 Hz), 7.18-7.15 (m, 1H), 7.03 (d, 2H, *J* = 8.7 Hz), 6.75 (d, 1H, *J* = 8.7 Hz), 4.62 (s, 2H), 4.86, 4.08 (ABq, 2H, *J* = 14.6 Hz), 4.27, 4.23 (ABq, 2H, *J* = 6.9 Hz), 3.77 (s, 3H), 3.45, 3.43 (ABq, 1H, *J* = 10.4 Hz), 3.17, 3.13 (ABq, 1H, *J* = 5.0 Hz), 2.76-2.68 (m, 1H), 2.57 (s, 3H), 2.22 (s, 3H), 2.39 (t, 2H, *J* = 5.0 Hz), 1.28 (td, 3H, *J* = 7.3 Hz, 2.3 Hz), 0.86 (t, 3H, *J* = 7.3 Hz). *R*_f = 0.32 in 33% acetone in hexanes.

-108-

Step F

[4-(1-[[[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl]-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester



5 Trifluoroacetic acid (70 mL, 1 mmol) was added dropwise to a solution of (4-{1-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-methyl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester and triethylsilane (23 mL, 144 mmol). The resulting solution was stirred at ambient temperature for 1h, and then concentrated *in vacuo*. The reaction residue was diluted with diethyl ether and washed with saturated
10 aqueous sodium bicarbonate and water. The organic layer was dried over sodium sulphate and concentrated *in vacuo*. $R_f=0.27$ in 33% acetone in hexanes.

1-Iodopropane (2.1 mL, 21.8 mmol) was added to a suspension of crude (4-{1-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-methyl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester and cesium carbonate (7.03 g, 21.8 mmol) in
15 dimethylformamide (100 mL). The resulting mixture was heated to 50 °C for 2h, then cooled to ambient temperature and diluted with diethyl ether. The organic layer was washed with 1N HCl, water, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by trituration, using acetone and hexanes, to provide 2.16 g (53%) of the title compound. $R_f=0.34$ in 33% acetone in hexanes. 1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 1H, $J = 2.2$ Hz), 7.73 (d, 1H, $J = 8.6$ Hz), 7.44 (dd, 1H, $J = 8.6$ Hz, 2.2 Hz), 7.22 (d, 1H, $J = 1.4$ Hz), 7.18 (dd, 1H, $J = 8.6$ Hz, 2.9 Hz), 6.59 (d, 1H, $J = 8.6$ Hz), 4.62 (s, 2H), 4.26 (q, 2H, $J = 7.2$ Hz), 3.38 (dd, 1H, $J = 14.4$ Hz, 9.4 Hz), 3.24 (dd, 1H, $J = 14.4$ Hz, 5.8 Hz), 3.20-3.06 (m, 3H), 2.56 (s, 3H), 2.24 (s, 3H), 1.97-1.87 (m, 1H), 1.52-1.35 (m, 3H), 1.29 (t, 3H, $J = 7.2$ Hz), 1.29 (t, 3H, $J = 7.2$ Hz), 1.09 (t, 3H, $J = 7.2$ Hz),
20 0.81 (t, 3H, $J = 7.2$ Hz).

-109-

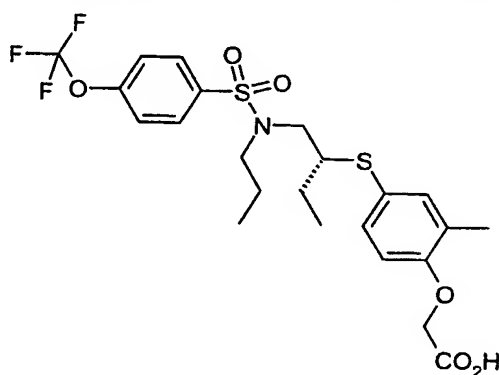
Step G

[4-(1-{{(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid

A solution of [4-(1-{{(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (2.16 g, 3.79 mmol) and 5N NaOH (2 mL) in ethanol (20 mL) was refluxed under nitrogen for 0.5h, cooled to ambient temperature, and concentrated in vacuo. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated *in vacuo* to provide 2.08 g (99%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.74 (s, 1H), 7.71 (d, 1H, *J* = 8.8 Hz, 1.5 Hz), 7.42 (d, 1H, *J* = 8.8 Hz), 7.22 (s, 1H), 7.19 (d, 1H, *J* = 8.8 Hz), 6.61 (d, 1H, *J* = 8.8 Hz), 5.29 (d, 1H, *J* = 2.2 Hz), 4.68 (s, 2H), 3.39 (dd, 1H, *J* = 13.9 hz, 8.8 Hz), 3.25 (dd, 1H, *J* = 15.4 Hz, 4.4 Hz), 3.20-3.07 (m, 3H), 2.57 (s, 3H), 2.22 (s, 3H), 1.96-1.86 (m, 1H), 1.53-1.35 (m, 3H), 1.09 (t, 3H, *J* = 7.3 Hz), 0.81 (t, 3H, *J* = 7.3 Hz). HRMS (ES⁺) *m/z* exact mass calculated for C₂₅H₃₁NO₅S₃Cl 556.1053, found 556.1038.

Example 21

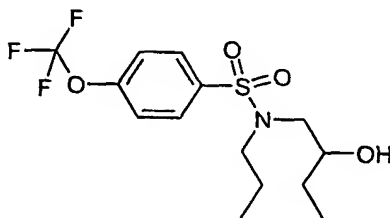
(*R*)-[2-Methyl-4-(1-{{propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-methyl}-propylsulfanyl)-phenoxy]-acetic acid



-110-

Step A

N-(2-hydroxy-butyl)-N-propyl-4-trifluoromethoxy-benzenesulfonamide



5

A 0°C solution of 1-amino-2-butanol (3.57 g, 40.0 mmol) and triethylamine (7.38 g, 72.9 mmol) in CH₂Cl₂ (100 mL) was treated with 4-(trifluoromethoxy) benzenesulfonyl chloride (9.50 g, 36.5 mmol) and the reaction warmed to room temperature and stirred for 1 hour under N₂. The reaction was quenched with 1 N HCl (75 mL) and diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 11.86 g (100%) of crude N-(2-hydroxy-butyl)-4-trifluoromethoxy-benzenesulfonamide that was utilized without purification.

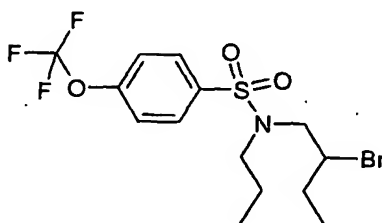
A solution of N-(2-hydroxy-butyl)-4-trifluoromethoxy-benzenesulfonamide (11.86 g, assume 36.5 mmol) and iodopropane (8.05 g, 47.4 mmol) in DMF (90 mL) was treated with cesium carbonate (15.44 g, 47.4 mmol) and the reaction mixture was stirred at room temperature for 17 hours under N₂. The reaction mixture was filtered using Et₂O to rinse the solids and the filtrate acidified with 1 N HCl (100 mL). The filtrate was diluted with more Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo* to afford crude product that was absorbed on silica gel and then column purified using 5/1 hexanes/acetone to afford 11.25 g (87%). R_f = 0.40 (1/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₁₄H₂₀O₄F₃NS 355, found 356 (M+1, 100%).

20

-111-

Step B

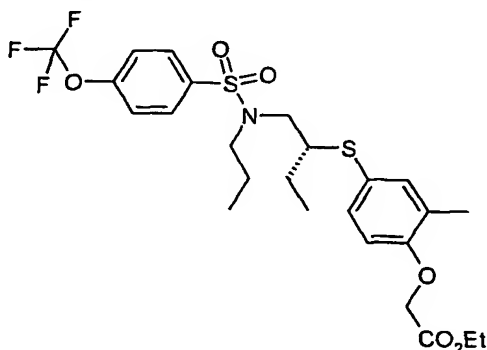
N-(2-Bromo-butyl)-N-propyl-4-trifluoromethoxy-benzenesulfonamide



- 5 A solution of N-(2-hydroxy-butyl)-N-propyl-4-trifluoromethoxy-benzenesulfonamide (11.23 g, 31.6 mmol) in CH₂Cl₂ (100 mL) was treated with carbon tetrabromide (15.72, 47.4 mmol) and then triphenylphosphine (12.43 g, 47.4 mmol). The reaction was stirred at room temperature under N₂ until the reaction was complete by TLC (2/1 hexanes/acetone). The solvent was removed *in vacuo* to afford crude product
- 10 that was triturated in Et₂O and filtered to remove most of the triphenylphosphine oxide. The solvent was removed *in vacuo* give crude product that was absorbed on silica gel and then column purified using 10/1 hexanes/acetone to afford 12.3 g (90%). R_f = 0.41 (2/1 hexanes/acetone).

Step C

- 15 (R)-[2-Methyl-4-(1-{{propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino}-methyl}-propylsulfanyl)-phenoxy]-acetic acid ethyl ester



- A solution of column purified (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (1.50 g, 6.62 mmol) in dry DMF (30 mL) was purged with N₂ and then 325 mesh K₂CO₃ (1.37 g, 9.91 mmol) was added and the resultant mixture purged with N₂ for
- 20 5 minutes more. A solution of (S)-N-(2-bromo-butyl)-N-propyl-4-trifluoromethoxy-benzenesulfonamide (3.45 g, 8.25 mmol) in DMF (15 mL) was added dropwise to the reaction, which was stirred for 5 hours at room temperature under N₂. The reaction was

-112-

acidified with 1 N HCl (20 mL), diluted with Et₂O and then extracted twice with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and then column purified using 8/1 hexanes/EtOAc to afford 3.1 g (73%) racemic. This material was resolved using
 5 preparative chiral HPLC (Chiralpak AD 8 x 34 cm, 95/5 heptane/EtOH, 375 ml/min, 230 nm UV setting) to give enantiomers (isomer 1, 99.3% ee, *R*; and isomer 2, 97.1% ee *S*). *R_f* isomer 1/isomer 2 = 0.42 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₅H₃₂O₆F₃NS₂ 563, found 564 (M + 1, 100%).

Step D

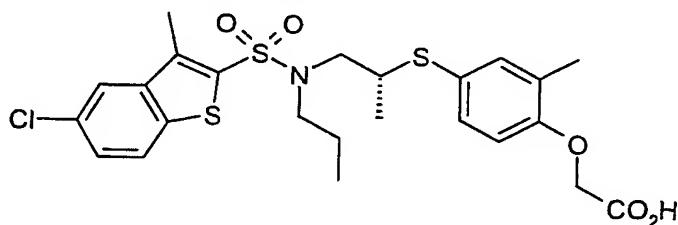
10 (*R*)-[2-Methyl-4-(1-{[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-methyl}-propylsulfanyl)-phenoxy]-acetic acid

A solution of (*R*)-[2-methyl-4-(1-{[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-methyl}-propylsulfanyl)-phenoxy]-acetic acid ethyl ester (1.40 g, 2.48 mmol) in EtOH (40 mL) was treated with 5 N NaOH (5 mL) and stirred at room
 15 temperature until saponification complete. The solvent was removed *in vacuo* to give a residue that was acidified with 1 N HCl and then diluted with EtOAc and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 1.31 g (98%). ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₃H₂₈O₆F₃NS₂Na 558.1200, found 558.1208.

20

Example 22

(*R*)-(4-{2-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

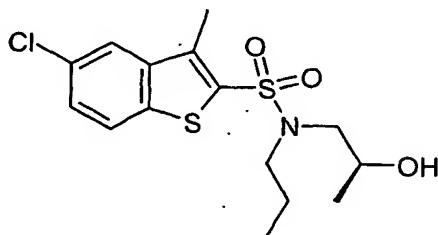


25

-113-

Step A

(S)-5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide



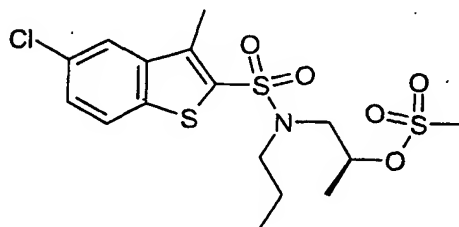
5 A 0 °C solution of (S)-(+)-1-amino-2-propanol (1.76 g, 23.4 mmol) and triethylamine (4.32 g, 42.7 mmol) in CH₂Cl₂ (100 mL) was treated with 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (6.0 g, 21.3 mmol) and the reaction warmed to room temperature and stirred for 1 hour under N₂. The reaction was quenched with 1 N HCl (50 mL), diluted with more CH₂Cl₂ and extracted with water. The organic
10 layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 6.86 g (100%) of crude 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide that was utilized without purification.

A solution of (S)-5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide (6.86 g, assume 21.3 mmol) and iodopropane (4.72 g, 27.8 mmol)
15 in DMF (90 mL) was treated with cesium carbonate (9.04 g, 27.7 mmol) and the reaction mixture was stirred at room temperature for 17 hours under N₂. The reaction mixture was filtered using Et₂O to rinse the solids and the filtrate acidified with 1 N HCl (50 mL). The filtrate was diluted with more Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo* to afford crude product that was
20 absorbed on silica gel and then column purified using 5/1 hexanes/acetone to afford 7.10 g (92%). R_f = 0.44 (1/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₅H₂₀O₃NS₂Cl 361, found 362 and 364 (M + 1 and M + 3, 100%).

-114-

Step B

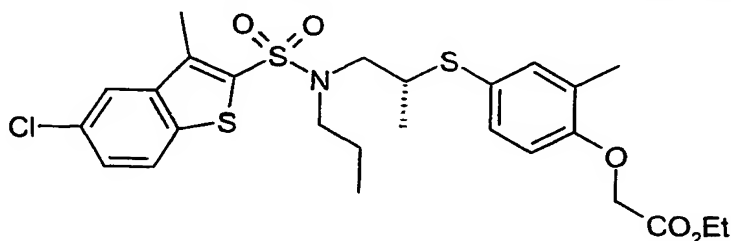
(*S*)-Methanesulfonic acid 2-[(5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester



5 A 0 °C solution of 5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (7.10 g, 19.6 mmol) and triethylamine (3.0 g, 29.6 mmol) in CH₂Cl₂ (100 mL) was treated with methanesulfonyl chloride (2.69 g, 23.5 mmol) and the reaction stirred for 2 hours at 0 °C under N₂. The reaction was quenched with 1 N HCl (40 mL) and diluted with more CH₂Cl₂ and extracted with water. The
10 organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo* to afford 9.27 g (100%) that was utilized without purification. *R*_f = 0.44 (1/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₆H₂₂O₅NS₃Cl 439, found 440 and 442 (*M* + 1 and *M* + 3, 100%).

Step C

15 (*R*)-(4-{2-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



A solution of column purified (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.205 g, 0.906 mmol) in dry DMF (40 mL) was purged with N₂ and then 325 mesh K₂CO₃ (0.188 g, 1.36 mmol) was added and the resultant mixture purged with N₂
20 for 5 minutes more. A solution of (*S*)-methanesulfonic acid 2-[(5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester (0.478 g, 1.09 mmol) in DMF (2 mL) was added dropwise to the reaction, which was stirred for 17 hours at room temperature under N₂. The reaction was acidified with 1 N HCl (20 mL), diluted

-115-

with Et₂O and then extracted twice with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and then column purified using 6/1 hexanes/EtOAc to afford 0.284 g (55%). *R_f* = 0.38 (2/1 hexanes/EtOAc). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₆H₃₂O₅NCIS₂ 569, found 570 and 572 (*M* + 1 and *M* + 3, 100%).

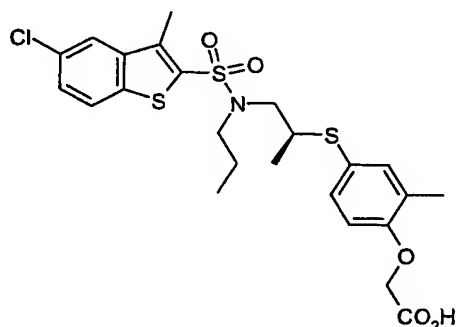
Step D

(*R*)-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

A solution of (*R*)-(4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (0.284 g, 0.498 mmol) in EtOH (10 mL) was treated with 5 N NaOH (1 mL) and stirred at room temperature until saponification complete. The solvent was removed *in vacuo* to give a residue that was acidified with 1 N HCl and then diluted with EtOAc and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo* to afford 0.281 g (100%). ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₄H₂₈O₅NCIS₂ 541, found 542 and 544 (*M* + 1 and *M* + 3, 100%).

Example 23

(*R*) and (*S*)-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



Racemic (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester was prepared as described in Example 22 and was then resolved using preparative chiral HPLC (Chiralcel OD 8 x 34 cm, 90/10 heptane/IPA. 370 ml/min, 250 nm UV setting) to give enantiomers (0.155 g, isomer 1, 100% ee, *R*: and 0.176 g, isomer 2, 100% ee, *S*). These

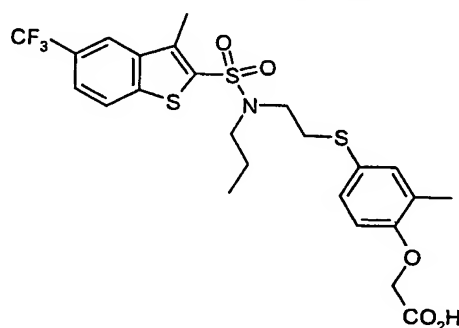
-116-

esters were saponified as described in Example 22, Step D to afford 0.136 g (93%, enantiomer 1) and 0.153 g (92%, enantiomer 2). ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calcd for $\text{C}_{24}\text{H}_{28}\text{O}_5\text{NClS}_3\text{Na}$ 564.0716, found 564.0718.

5

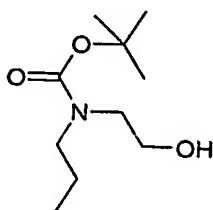
Example 24

(2-Methyl-4-{2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Step A

10

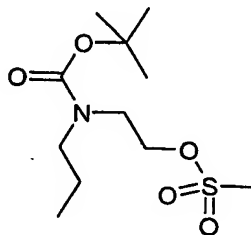
(2-Hydroxy-ethyl)-propyl-carbamic acid *tert*-butyl ester



A 0 °C solution of 2-propylamino-ethanol (3.00 g, 29.1 mmol) and triethylamine (3.09 g, 30.5 mmol) in dry THF (60 mL) was treated dropwise with a solution of di-*tert*-butyl carbonate (6.66 g, 30.5 mmol) in THF (10 mL). The reaction was stirred and warmed to room temperature for 1.5 hours under N_2 . The reaction was diluted with EtOAc and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 6.11 g (100%) of crude product that was utilized without purification. R_f = 0.46 (1/1 hexanes/acetone, CAM stain). ^1H NMR (400 MHz, CDCl_3) δ 3.75-3.71 (m, 2H), 3.41-3.37 (m, 2H), 3.18 (bt, 2H, J = 6.85 Hz), 1.59-1.50 (m, 2H), 1.46 (s, 9H), 0.875 (t, 3H, J = 7.33 Hz).

20

-117-

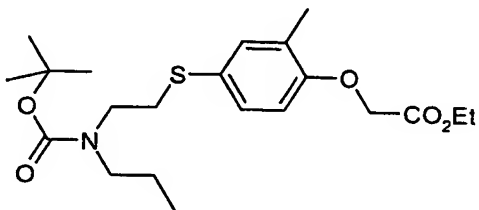
Step BMethanesulfonic acid 2-(*tert*-butoxycarbonyl-propyl-amino)-ethyl ester

5 A 0 °C solution of (2-hydroxy-ethyl)-propyl-carbamic acid *tert*-butyl ester (3.0 g, 14.8 mmol) and triethylamine (2.40 g, 23.7 mmol) in CH₂Cl₂ (30 mL) was treated with methanesulfonyl chloride (2.22 g, 19.4 mmol) and the reaction stirred for 1.5 hours at 0 °C under N₂. The reaction was quenched with 1 N HCl (40 mL) and diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (MgSO₄) and the solvent was removed *in vacuo* to afford 4.11 g (99%) that was utilized without

10 purification. R_f = 0.58 (1/1 hexanes/acetone, CAM stain). ¹H NMR (400 MHz, CDCl₃) δ 4.34-3.30 (m, 2H), 3.57-3.49 (m, 2H), 3.24-3.13 (m, 2H), 3.00 (s, 3H), 1.72-1.51 (m, 2H), 1.45 (s, 9H), 0.875 (t, 3H, *J* = 7.58 Hz).

Step C

15 ({4-[2-(*tert*-Butoxycarbonyl-propyl-amino)-ethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester



A solution of crude (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (3.95 g, 17.5 mmol) in dry DMF (35 mL) was purged with N₂ and then Cs₂CO₃ (7.12 g, 21.9 mmol) was added and the resultant mixture purged with N₂ for 5 minutes more. A

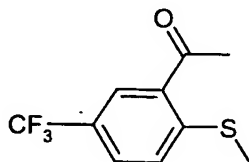
20 solution of methanesulfonic acid 2-(*tert*-butoxycarbonyl-propyl-amino)-ethyl ester (4.10 g, 14.6 mmol) in DMF (5 mL) was added dropwise to the reaction and it was heated to 50 °C and stirred for 17 hours under N₂. The reaction was cooled and filtered using Et₂O to rinse the solids. The filtrate was acidified with 1 N HCl (15 mL), diluted with Et₂O and then extracted twice with water. The organic layer was dried (Na₂SO₄) and the

-118-

solvent removed *in vacuo* to afford crude product that was absorbed on silica gel and then column purified using 6/1 hexanes/acetone to afford 3.25 g (54%). $R_f = 0.33$ (2/1 hexanes/acetone).

Step D

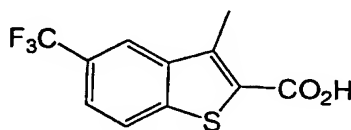
1-(2-Methylsulfanyl-5-trifluoromethyl-phenyl)-ethanone



A solution of 2-fluoro-5-trifluoromethyl acetophenone (3.0 g, 14.5 mmol) in dry DMF (20 mL) was treated with sodium thiomethoxide (1.22 g, 17.4 mmol) and the reaction was stirred for 2 hours at room temperature under N_2 . The reaction was quenched with 1 N HCl (10 mL), diluted with Et_2O and then extracted twice with water. The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford crude product that was absorbed on silica gel and then column purified using 5/1 hexanes/acetone to afford 2.88 g (85%). $R_f = 0.57$ (1/1 hexanes/acetone). 1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.69 (d, 1H, $J = 8.31$ Hz), 7.42 (d, 1H, $J = 8.80$ Hz), 2.68 (s, 3H), 2.48 (s, 3H).

Step E

3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid

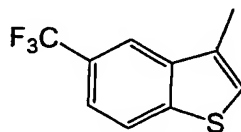


A mixture of 1-(2-methylsulfanyl-5-trifluoromethyl-phenyl)-ethanone (2.06 g, 8.79 mmol) and bromoacetic acid (7.33 g, 52.8 mmol) in acetic acid (20 mL) was heated to reflux and stirred for 20 hours under N_2 . The reaction was cooled and water was added to form a slurry. The slurry was filtered and the solids rinsed with water to afford 1.59 g (69%) of the title compound after drying in a vacuum oven at 45 $^{\circ}C$. $R_f = 0.18$ (1/1 hexanes/acetone). 1H NMR (400 MHz, $CDCl_3$). MS (ES $^-$) m/z mass calculated for $C_{11}H_7O_2SF_3$ 260. found 259 (M - 1, 100%).

-119-

Step F

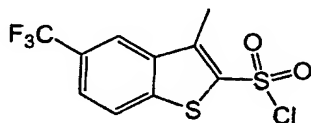
3-Methyl-5-trifluoromethyl-benzo[b]thiophene



A mixture of 3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid (0.80 g, 3.07 mmol) and copper powder (0.164 g, 2.58 mmol) in quinoline (14 mL) was placed in a 200 °C oil bath and stirred for 20 minutes under N₂. The reaction was cooled, diluted with CH₂Cl₂ and filtered through hyflo. The filtrate was extracted twice with 1 N HCl (100 mL) then water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was column purified using 100% hexanes to afford 0.575 g (86%). R_f = 0.62 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃).

Step G

3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl chloride

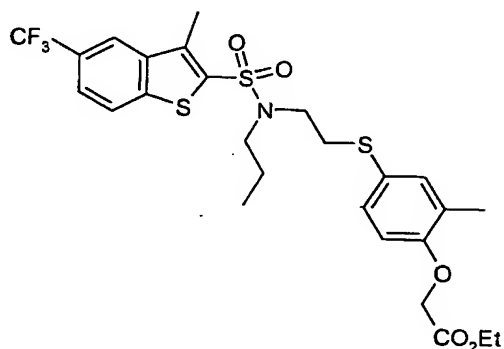


A 0 °C solution of 3-methyl-5-trifluoromethyl-benzo[b]thiophene (0.558 g, 2.58 mmol) in CH₂Cl₂ (4 mL) was treated dropwise with chlorosulfonic acid (0.894 g, 7.67 mmol) in CH₂Cl₂ (4 mL). The reaction was warmed to room temperature and stirred for 1.5 hours under N₂. The reaction was poured into ice water and the mixture extracted with Et₂O. The aqueous layer was re-extracted with CH₂Cl₂ and the combined organic layers were dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.22 g (27%) as a gray solid that was utilized without purification. R_f = 0.46 (2/1 hexanes/acetone).

-120-

Step H

(2-Methyl-4-{2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester



5 A 0 °C solution of ({4-[2-(*tert*-butoxycarbonyl-propyl-amino)-ethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (0.11 g, 0.266 mmol) and dimethylethyl silane (0.071 g, 0.805 mmol) in dry CH₂Cl₂ (3 mL) was treated with trifluoroacetic acid (0.5 mL) and warmed to room temperature and stirred for 1.5 hours under N₂. The solvent was removed *in vacuo* to afford the trifluoroacetic acid salt of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester, which was
10 carried on without purification.

The [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester- TFA salt was re-dissolved in CH₂Cl₂ (5 mL) and cooled to 0 °C. Triethylamine (0.162 g, 1.60 mmol) was added dropwise to the reaction and then a solution of 3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl chloride (0.084 g, 0.266 mmol) in CH₂Cl₂ (3 mL) was added. The reaction was warmed to room temperature and stirred for 1 hour under N₂. The reaction was acidified with 1 N HCl (10 mL), diluted with CH₂Cl₂ and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and then column
15 purified using 6/1 hexanes/acetone to afford 0.113 g (72%). R_f = 0.18 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₆H₃₀O₅NS₃F₃ 589, found 590 (M + 1, 100%).
20

-121-

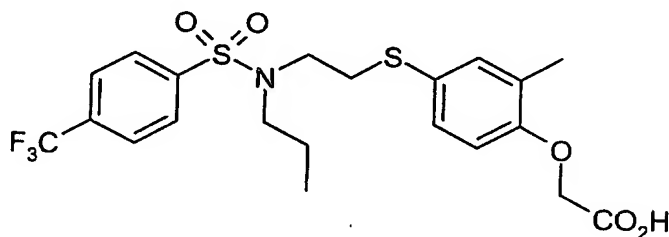
Step I

(2-Methyl-4-{2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

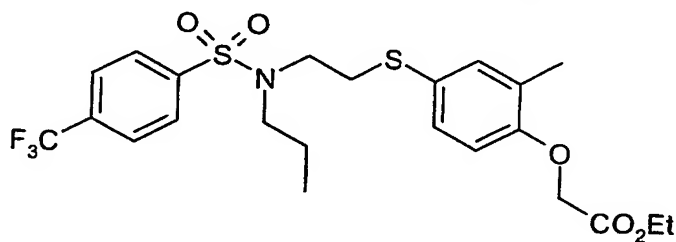
A 0 °C solution of (2-methyl-4-{2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester (0.113 g, 0.192 mmol) in THF (6 mL) was treated with 1 N LiOH (0.57 mL) and stirred at room temperature until saponification complete. The mixture was acidified with 1 N HCl and then diluted with EtOAc and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.079 g (73%). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₄H₂₆O₅NS₃F₃ 561, found 562 (M + 1, 100%).

Example 25

(2-Methyl-4-{2-[propyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Step A

((2-Methyl-4-{2-[propyl-(4-trifluoromethylbenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester



Procedure from Example 24, Step H was utilized with 4-trifluoromethyl-benzenesulfonyl chloride to afford 0.132 g (80%). R_f = 0.34 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₃H₂₈O₅NS₂F₃ 519, found 520 (M + 1, 100%).

-122-

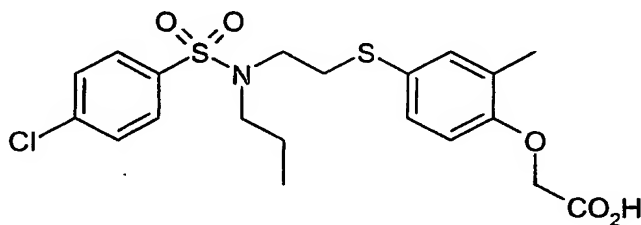
Step B

(2-Methyl-4-{2-[propyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 24, Step 1 was utilized with ((2-methyl-4-{2-[propyl-(4-trifluoromethylbenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester to afford 0.094 g (76%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{21}\text{H}_{24}\text{O}_5\text{NS}_2\text{F}_3\text{Na}$ 514.0946, found 514.0928.

Example 26

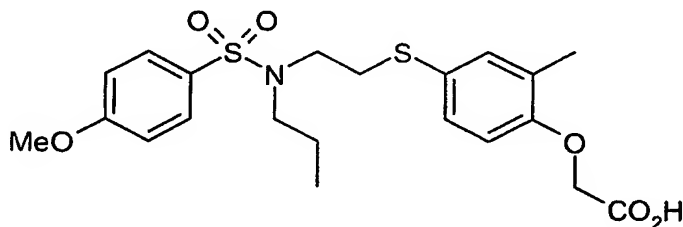
((4-{2-[(4-Chloro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



Procedure from Example 25 was utilized with 4-chloro-benzenesulfonyl chloride to afford 0.80 g (89%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{NS}_2\text{ClNa}$ 480.0682, found 480.0683.

Example 27

(4-{2-[(4-Methoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

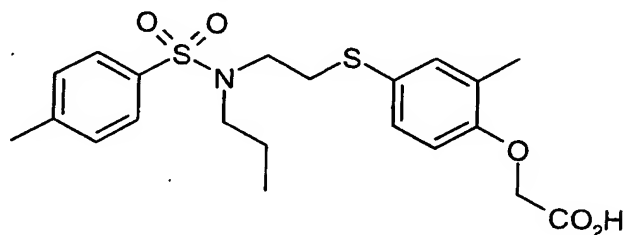


Procedure from Example 25 was utilized with 4-methoxy-benzenesulfonyl chloride to afford 0.105 g acid that was purified by preparative HPLC to afford 0.027 g (22%) of the title compound. ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{21}\text{H}_{27}\text{O}_6\text{NS}_2$ 453, found 454 ($\text{M}+1$, 100%).

-123-

Example 28

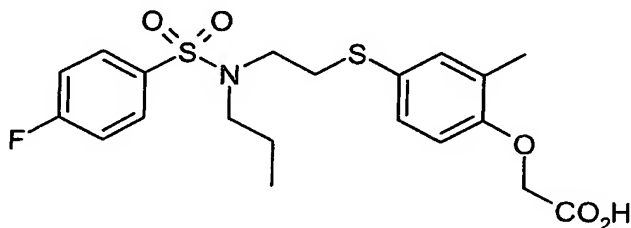
(2-Methyl-4-{2-[propyl-(toluene-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



Procedure from Example 25 was utilized with 4-methyl-benzenesulfonyl chloride to afford 0.139 g acid that was purified by preparative HPLC to afford 0.040 g (34%) of the title compound. ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{21}\text{H}_{27}\text{O}_5\text{NS}_2$ 437, found 438 ($\text{M}+1$, 100%).

Example 29

(4-{2-[(4-Fluoro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

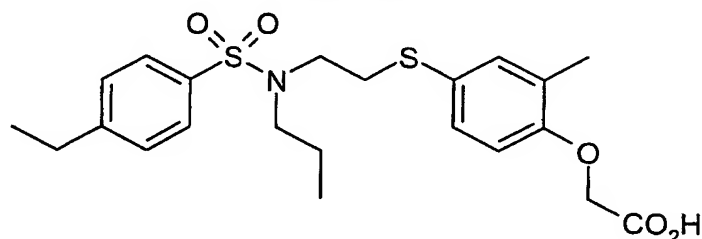


Procedure from Example 25 was utilized with 4-fluoro-benzenesulfonyl chloride to afford 0.146 g acid that was purified by preparative HPLC to afford 0.045 g (38%) of the title compound. ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{NS}_2$ 441, found 442 ($\text{M}+1$, 100%).

-124-

Example 30

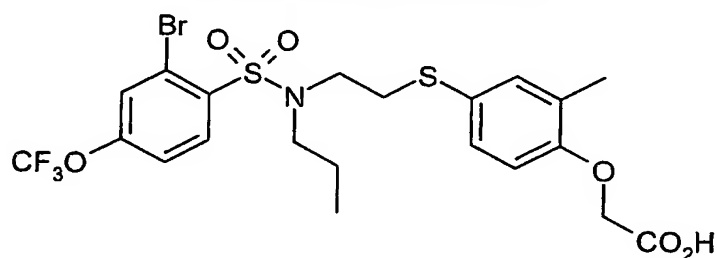
(4-{2-[(4-Ethyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



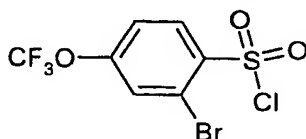
Procedure from Example 25 was utilized with 4-ethyl-benzenesulfonyl chloride to afford 0.086 g acid that was purified by preparative HPLC to afford 0.058 g (48%) of the title compound. ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{22}\text{H}_{30}\text{O}_5\text{NS}_2$ 452.1565, found 452.179.

Example 31

(4-{2-[(2-Bromo-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

2-Bromo-4-trifluoromethoxy-benzenesulfonyl chloride



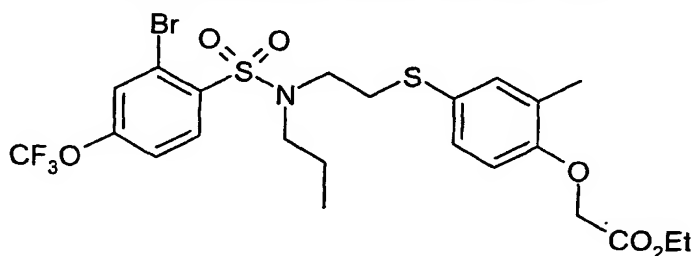
Chlorosulfonic acid (8 mL) was cooled to 0°C and was treated with 1-bromo-3-(trifluoromethoxy)benzene (5.0 g, 20.7 mmol). The resultant mixture was stirred for 10 minutes at 0°C and then warmed to room temperature and stirred for 1 hour under N_2 . The reaction mixture was poured into ice water and then extracted twice with CH_2Cl_2 . The organic layer was dried (MgSO_4) and the solvent was removed *in vacuo* to

-125-

afford 2.69 g (38%) that was utilized without further purification. $R_f = 0.53$ (2/1 hexanes/acetone).

Step B

- 5 (4-{2-[(2-Bromo-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



Procedure from Example 24, Step H was utilized with 2-bromo-4-trifluoromethoxy-benzenesulfonyl chloride to afford 0.65 g (87%) of the title compound.
 10 $R_f = 0.31$ (2/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{23}\text{H}_{27}\text{O}_6\text{NS}_2\text{F}_3\text{Br}$ 613, found 614 and 616 ($M + 1$ and $M + 3$, 100%).

Step C

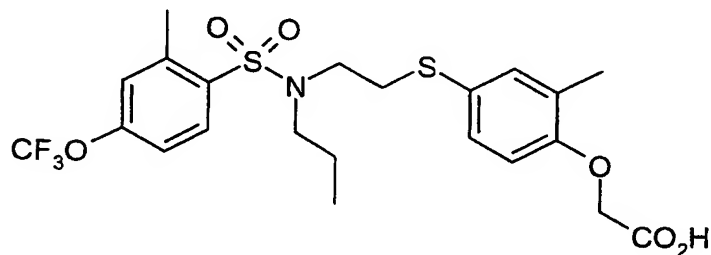
- (4-{2-[(2-Bromo-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

15 A solution of (4-{2-[(2-bromo-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (0.056 g, 0.091 mmol) in EtOH (6 mL) was treated with 5 N NaOH (0.5 mL) and was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* to give a residue that was acidified with 1 N HCl (10 mL), diluted with ethyl acetate and extracted with water. The
 20 organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford 0.072 g of crude acid that was purified by preparative HPLC to afford 0.042 g (79%). ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{21}\text{H}_{24}\text{NO}_6\text{S}_2\text{F}_3\text{Br}$ 586.0181, found 586.0164.

-126-

Example 32

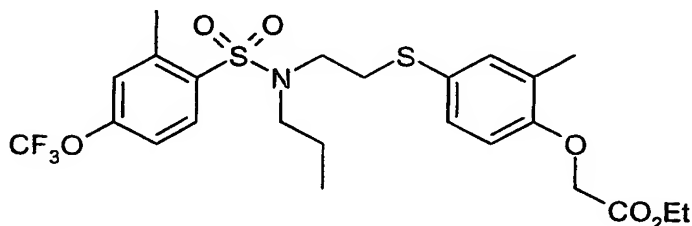
((2-Methyl-4-{2-[(2-methyl-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid



5

Step A

(2-Methyl-4-{2-[(2-methyl-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester



The compound of (4-{2-[(2-bromo-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (Example 31, Step B) (0.100 g, 0.163 mmol), methyl boronic acid (0.029 g, 0.484 mmol) and cesium fluoride (0.087 g, 0.573 mmol) were combined in 1,4-dioxane (3 mL) and purged with N₂. The reaction was treated with 1,1'-bis(diphenylphosphino)ferrocene palladium (II)chloride, CH₂Cl₂ complex (0.018 g, 0.025 mmol) and heated in an oil bath at 80 °C for 2 hours under N₂. The reaction was cooled and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and column purified using 6/1 hexanes/acetone to afford 0.080 g (91%). R_f = 0.22 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₄H₃₀O₆NS₂F₃ 549, found 550 (M + 1, 100%).

20

-127-

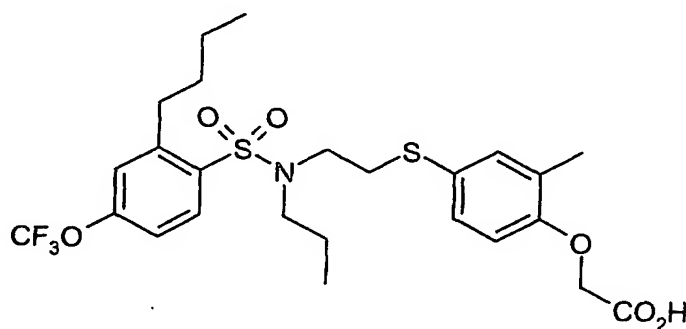
Step B

((2-Methyl-4-{2-[(2-methyl-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

A solution of (2-methyl-4-{2-[(2-methyl-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester (0.080 g, 0.156 mmol) in EtOH (6 mL) was treated with 5 N NaOH (0.5 mL) and was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* to give a residue that was acidified with 1 N HCl (10 mL) and then diluted with ethyl acetate and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.053 g of crude acid that was purified by preparative HPLC to afford 0.048 g (63%). ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₂H₂₇NO₆S₂F₃ 522.1232, found 522.1252.

Example 33

(4-{2-[(2-Butyl-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



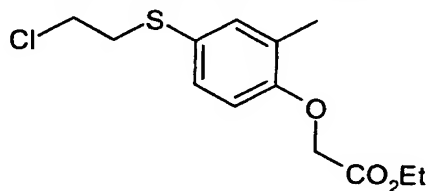
The compound of (4-{2-[(2-bromo-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (Example 31, Step B) (0.126 g, 0.205 mmol), butyl boronic acid (0.063 g, 0.618 mmol) and cesium fluoride (0.109 g, 0.718 mmol) were combined in 1,4-dioxane (4 mL) and purged with N₂. The reaction was treated with 1,1'-bis(diphenylphosphino)ferrocene palladium (II)chloride, CH₂Cl₂ complex (0.023 g, 0.031 mmol) and heated in an oil bath at 80 °C for 4 hours under N₂. The reaction was cooled and the solvent removed *in vacuo* to afford 0.172 g (assume 0.205 mmol) of crude (4-{2-[(2-butyl-4-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester

-128-

that was dissolved in EtOH (6 mL) and treated with 5 N NaOH (0.5 mL). The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* to give a residue that was acidified with 1 N HCl (10 mL) and then diluted with ethyl acetate and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.133 g of crude acid that was purified by preparative HPLC to afford 0.011 g (9%). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₅H₃₂NO₆S₂F₃ 563, found 564 (M + 1, 100%).

Example 34

[4-(2-Chloro-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester

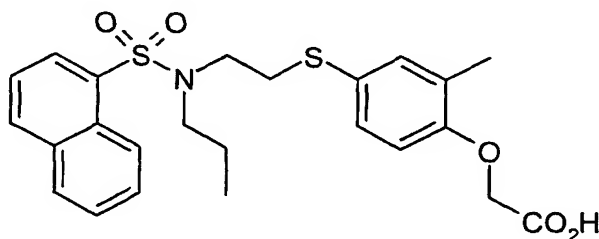


A solution of crude (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (1.64 g, 7.25 mmol) in dry DMF (20 mL) was purged with N₂ and then 325 mesh K₂CO₃ (1.50 g, 10.9 mmol) was added and the resultant mixture purged with N₂ for 5 minutes more. 1-Bromo-2-chloroethane (3.11 g, 21.7 mmol) was added dropwise to the reaction, which was stirred for 17 hours at room temperature under N₂. The reaction was acidified with 1 N HCl (20 mL), diluted with Et₂O and then extracted twice with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 1.60 g (77%) that was utilized without further purification. R_f = 0.60 (1/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₃H₁₇O₃ClS 288, found 289 and 291 (M + 1 and M + 3, 100%).

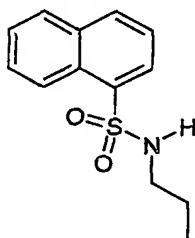
-129-

Example 35

(2-Methyl-4-{2-[(naphthalene-1-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Step A

Naphthalene-1-sulfonic acid propylamide



A solution of propyl amine (0.051 g, 0.862 mmol) and triethylamine (0.134 g, 1.32 mmol) in CH_2Cl_2 (6 mL) was treated with naphthalene-1-sulfonyl chloride (0.150 g, 0.660 mmol) and stirred overnight at room temperature under N_2 . The reaction mixture was gravity filtered through a Varian Extube Extraction Column (ChemElut 1005) that had been pre-treated with 4 mL 1 N HCl. The extraction column was washed with CH_2Cl_2 (4X), and the solvent was removed from the filtrate *in vacuo* to afford 0.157 g (95%) that was utilized without further purification. $R_f = 0.47$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{13}\text{H}_{15}\text{O}_2\text{NS}$ 249, found 250 ($\text{M} + 1$, 100%).

Step B

(2-Methyl-4-{2-[(naphthalene-1-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

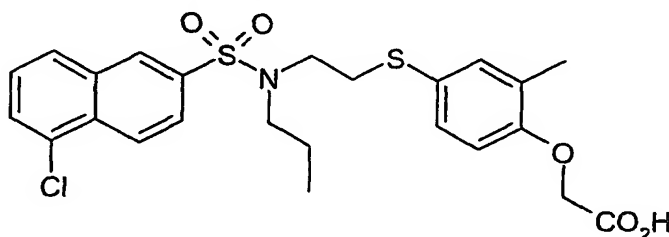
A mixture of [4-(2-chloro-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.097 g, 0.334 mmol), naphthalene-1-sulfonic acid propylamide (0.084 g, 0.337 mmol) and Cs_2CO_3 (0.143 g, 0.439 mmol) in DMF (5 mL) was stirred for 18 hours at 60°C . The reaction was cooled to room temperature and treated with 5 N NaOH (1.5 mL) and stirred for 2 hours at room temperature. The reaction was acidified with 1 N

-130-

HCl (20 mL), diluted with Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.237 g crude product that was purified by preparative HPLC to afford 0.013 g (8%) of the title compound. ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₄H₂₈O₅NS₂ 474.1409, found 474.1412.

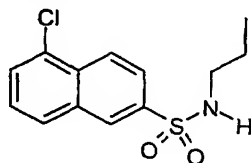
Example 36

(4-{2-[(5-Chloro-naphthalene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid



Step A

5-Chloro-naphthalene-2-sulfonic acid propylamide



Procedure from Example 35. Step A was utilized with 5-chloro-naphthalene-2-sulfonyl chloride to afford 0.160 g (98%) that was utilized without further purification. R_f = 0.53 (1/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calcd for C₁₃H₁₄O₂NCIS 283, found 284 and 286 (M + 1 and M + 3, 100%).

-131-

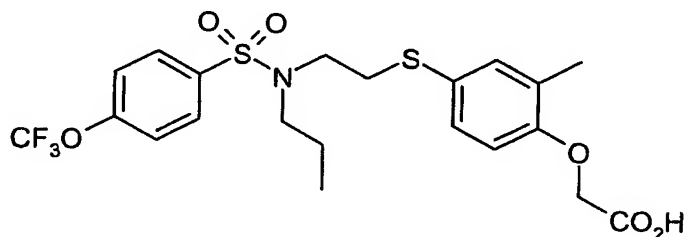
Step B

(4-{2-[(5-Chloro-naphthalene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

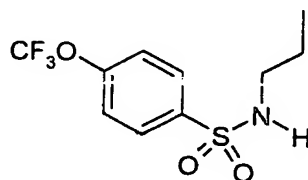
Procedure from Example 35, Step B was utilized to afford 0.009 g (7%) of the title compound. ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₄H₂₇O₅NS₂Cl 508.1019, found 508.1000.

Example 37

(2-Methyl-4-{2-[propyl-(4-trifluoromethoxybenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Step A

N-Propyl-4-trifluoromethoxy-benzenesulfonamide



Procedure from Example 35, Step A was utilized with 4-trifluoromethoxy-benzenesulfonyl chloride to afford 0.154 g (94%) that was utilized without further purification. *R_f* = 0.53 (1/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calcd for C₁₀H₁₂O₃NSF₃ 283, found 284 (M + 1, 100%).

Step B

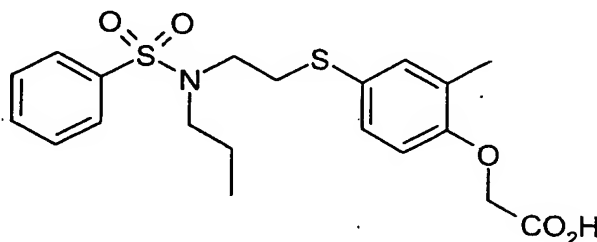
(2-Methyl-4-{2-[propyl-(4-trifluoromethoxybenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 35. Step B was utilized to afford 0.008 g (6%) of the title compound. ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₁H₂₅O₆NS₂F₃ 508.1075, found 508.1100.

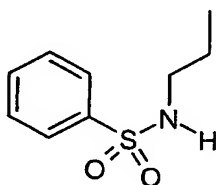
-132-

Example 38

{4-[2-(Benzenesulfonyl-propyl-amino)-ethylsulfanyl]-2-methyl-phenoxy}-acetic acid

Step A

N-Propyl-benzenesulfonamide



Procedure from Example 35, Step A was utilized with benzenesulfonyl chloride to afford 0.169 g (100%) that was utilized without further purification. $R_f = 0.48$ (1/1 hexanes/acetone). $^1\text{H NMR}$ (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_9\text{H}_{13}\text{O}_2\text{NS}$ 199, found 200 ($M+1$, 100%).

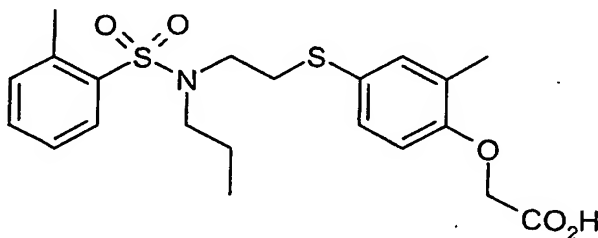
Step B

{4-[2-(Benzenesulfonyl-propyl-amino)-ethylsulfanyl]-2-methyl-phenoxy}-acetic acid

Procedure from example 15, Step B utilized to afford 0.008 g (4%) of the title compound. $^1\text{H NMR}$ (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{20}\text{H}_{26}\text{O}_5\text{NS}_2$ 424.1252, found 424.1241.

Example 39

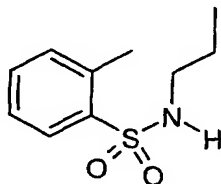
(2-Methyl-4-{2-[propyl-(toluene-2-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



-133-

Step A

2-Methyl-N-propyl-benzenesulfonamide .



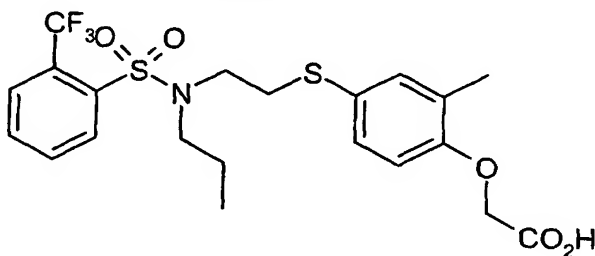
5 Procedure from Example 35, Step A was utilized with 2-methyl benzenesulfonyl chloride to afford 0.167 g (100%) that was utilized without further purification. $R_f = 0.48$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calcd for $\text{C}_{10}\text{H}_{15}\text{O}_2\text{NS}$ 213, found 214 ($\text{M} + 1$, 100%).

Step B

10 (2-Methyl-4-{2-[propyl-(toluene-2-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid
Procedure from Example 35, Step B utilized to afford 0.011 g (6%) of the
title compound. ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for
C₂₁H₂₈O₅NS₂ 438.1409, found 438.1427.

Example 40

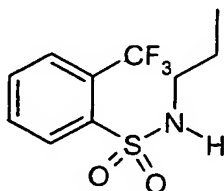
15 (2-Methyl-4-{2-[propyl-(2-trifluoromethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-
phenoxy)-acetic acid



-134-

Step A

N-Propyl-2-trifluoromethyl-benzenesulfonamide



5 Procedure from Example 35, Step A was utilized with 2-trifluoromethyl-benzenesulfonyl chloride to afford 0.164 g (100%) that was utilized without further purification. $R_f = 0.48$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{NSF}_3$ 267, found 268 ($M + 1$, 100%).

Step B

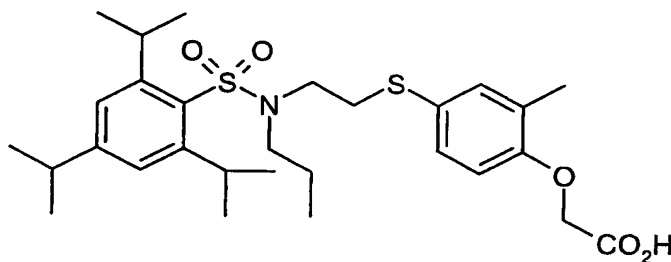
10 (2-Methyl-4-{2-[propyl-(2-trifluoromethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 35, Step B utilized to afford 0.010 g (9%) of title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{21}\text{H}_{25}\text{O}_5\text{NS}_2\text{F}_3$ 492.1126, found 492.1146.

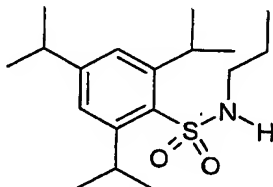
15

Example 41

(2-Methyl-4-{2-[propyl-(2,4,6-triisopropylbenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



-135-

Step A2,4,6-Triisopropyl-*N*-propyl-benzenesulfonamide

5 Procedure from Example 35, Step A was utilized with 2,4,6-triisopropyl-benzenesulfonyl chloride to afford 0.161 g (100%) that was utilized without further purification. $R_f = 0.63$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{18}\text{H}_{31}\text{O}_2\text{NS}$ 325, found 326 ($\text{M} + 1$, 100%).

Step B

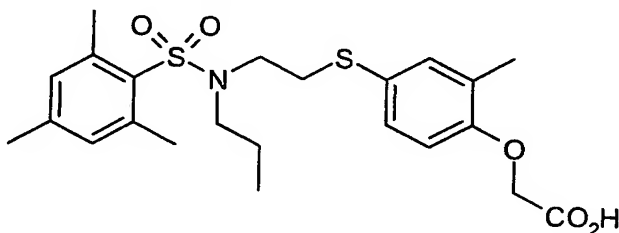
10 (2-Methyl-4-{2-[propyl-(2,4,6-triisopropylbenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 35, Step B utilized to afford 0.009 g (7%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{29}\text{H}_{44}\text{O}_5\text{NS}_2$ 550.2661, found 550.2667.

15

Example 42

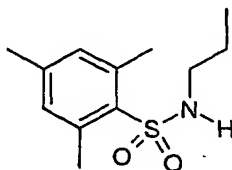
(2-Methyl-4-{2-[propyl-(2,4,6-trimethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



-136-

Step A

2,4,6-Trimethyl-N-propyl-benzenesulfonamide



5 Procedure from Example 35, Step A was utilized with 2,4,6-trimethyl-benzenesulfonyl chloride to afford 0.165 g (100%) that was utilized without further purification. $R_f = 0.51$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{12}\text{H}_{19}\text{O}_2\text{NS}$ 241, found 242 ($\text{M} + 1$, 100%).

Step B

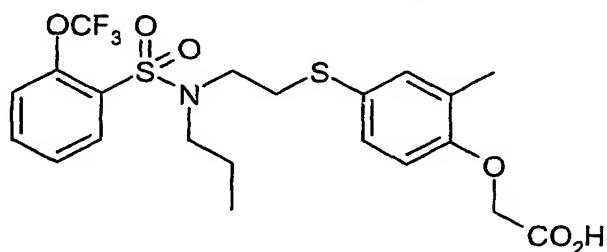
10 (2-Methyl-4-{2-[propyl-(2,4,6-trimethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 35, Step B utilized to afford 0.012 g (9%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{23}\text{H}_{32}\text{O}_5\text{NS}_2$ 466.1722, found 466.1735.

15

Example 43

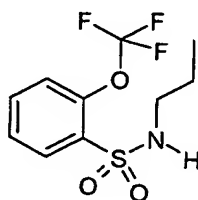
(2-Methyl-4-{2-[propyl-(2-trifluoromethoxybenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



-137-

Step A

N-Propyl-2-trifluoromethoxy-benzenesulfonamide



5 Procedure from Example 35, Step A was utilized with 2-trifluoromethoxy-benzenesulfonyl chloride to afford 0.163 g (100%) that was utilized without further purification. $R_f = 0.51$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{NSF}_3$ 283, found 284 ($M + 1$, 100%).

Step B

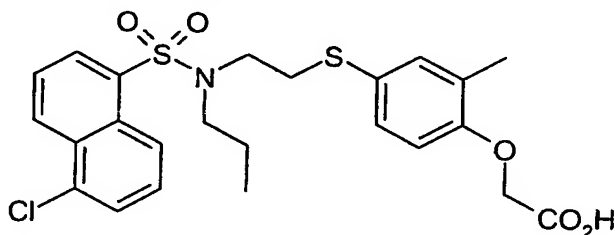
10 (2-Methyl-4-{2-[propyl-(2-trifluoromethoxybenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 35, Step B utilized to afford 0.008 g (7%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{21}\text{H}_{24}\text{O}_6\text{NS}_2\text{F}_3\text{Na}$ 530.0895, found 530.0889.

15

Example 44

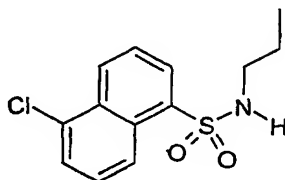
(4-{2-[(5-Chloro-naphthalene-1-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



-138-

Step A

5-Chloro-naphthalene-1-sulfonic acid propylamide



5 Procedure from Example 35, Step A was utilized with 5-chloro-naphthalene-1-sulfonyl chloride to afford 0.163 g (100%) that was utilized without further purification. $R_f = 0.54$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{NSCl}$ 283, found 284 and 286 ($M + 1$ and $M + 3$, 100%).

Step B

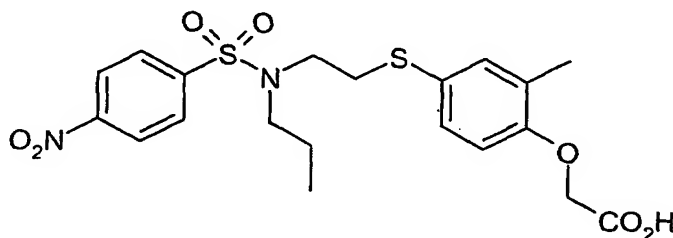
10 (4-{2-[(5-Chloro-naphthalene-1-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid

Procedure from Example 35, Step B utilized to afford 0.011 g (9%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{24}\text{H}_{27}\text{O}_5\text{NS}_2\text{Cl}$ 508.1019, found 508.1021.

15

Example 45

(2-Methyl-4-{2-[(4-nitro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

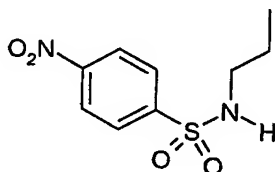


20

-139-

Step A

4-Nitro-N-propyl-benzenesulfonamide



5 Procedure from Example 35, Step A was utilized with 4-nitro-benzenesulfonyl chloride to afford 0.165 g (100%) that was utilized without further purification. $R_f = 0.49$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^-) m/z mass calcd for $\text{C}_9\text{H}_{12}\text{O}_3\text{N}_2\text{S}$ 244, found 243 ($M - 1$, 100%).

Step B

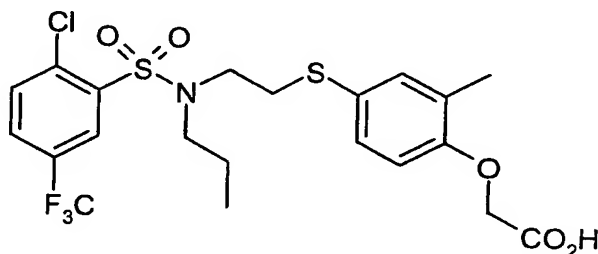
10 (2-Methyl-4-{2-[(4-nitro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 35, Step B utilized to afford 0.008 g (6%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{20}\text{H}_{25}\text{O}_7\text{N}_2\text{S}_2$ 469.1103, found 469.1113.

15

Example 46

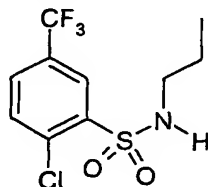
(4-{2-[(2-Chloro-5-trifluoromethyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



-140-

Step A

2-Chloro-N-propyl-5-trifluoromethyl-benzenesulfonamide



5 Procedure from Example 35, Step A was utilized with 2-chloro-5-trifluoromethyl-benzenesulfonyl chloride to afford 0.162 g (94%) that was utilized without further purification. $R_f = 0.53$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{10}\text{H}_{11}\text{O}_2\text{NSClF}_3$ 301, found 302 and 304 ($\text{M}+1$ and $\text{M}+3$, 100%).

Step B

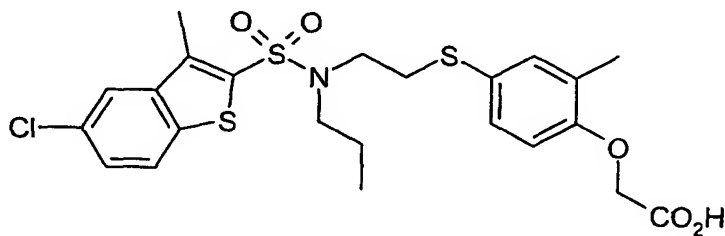
10 (4-{2-[(2-Chloro-5-trifluoromethyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Procedure from Example 35, Step B utilized to afford 0.014 g (12%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{21}\text{H}_{24}\text{O}_5\text{NS}_2\text{F}_3\text{Cl}$ 526.0737, found 526.0724.

15

Example 47

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

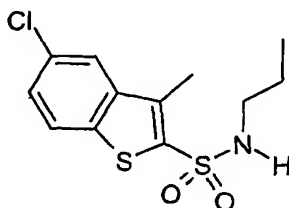


20

-141-

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid propylamide



A 0 °C solution of propylamine (0.35 g, 5.92 mmol) and triethylamine (1.08 g, 10.7 mmol) in CH₂Cl₂ (75 mL) was treated with 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (1.50 g, 5.33 mmol) and stirred at room temperature under N₂. When the reaction was complete by TLC (1/1 hexanes/acetone) the reaction was quenched with 1 N HCl (21 mL), diluted with water and extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 1.61 g (99%) that was utilized without further purification. *R*_f = 0.53 (1/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₂H₁₄O₂NS₂Cl 303, found 304 and 306 (M + 1 and M + 3, 100%).

Step B

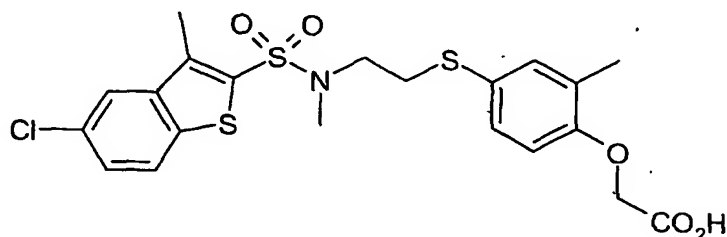
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

A mixture of [4-(2-chloro-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.116 g, 0.401 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid propylamide (0.122 g, 0.401 mmol) and Cs₂CO₃ (0.170 g, 0.520 mmol) in DMF (6 mL) was stirred for 17 hours at room temperature under N₂. The reaction was heated to 40 °C for 4 hours more and then cooled to room temperature. The reaction mixture was treated with 5 N NaOH (1.5 mL) and stirred for 2 hours at room temperature. The reaction was acidified with 1 N HCl (20 mL), diluted with Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.282 g crude product that was purified by preparative HPLC to afford 0.013 g (7%). ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₃H₂₆O₅NCIS₃Na 550.0559, found 550.0563.

-142-

Example 48

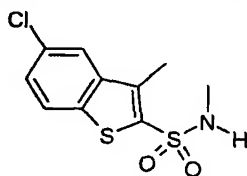
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-methyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid methylamide



A solution of triethylamine (1.38 g, 7.17 mmol) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (1.00 g, 3.56 mmol) in THF (10 mL) was treated with a 2 M solution of methylamine in THF (2.67 mL, 5.35 mmol) and stirred at room temperature under N₂ for 30 minutes. When the reaction was complete by TLC (1/1 hexanes/acetone) the reaction was quenched with 1 N HCl (14 mL), diluted with water and extracted with ethyl acetate. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.97 g (99%) that was utilized without further purification. R_f = 0.47 (1/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁻) *m/z* mass calculated for C₁₀H₁₀O₂NS₂Cl 275. found 274 and 276 (M-1 and M+1, 100%).

Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-methyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

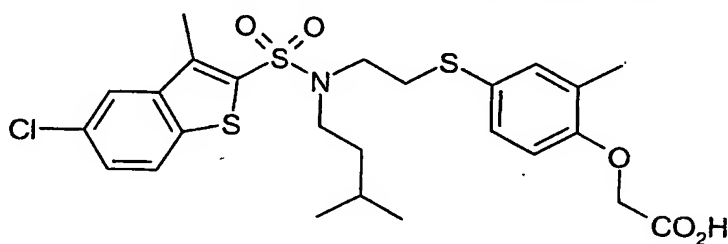
A mixture of [4-(2-chloro-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.116 g, 0.401 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid methylamide (0.110 g, 0.401 mmol) and Cs₂CO₃ (0.170 g, 0.520 mmol) in DMF (6 mL) was stirred for 17 hours at room temperature under N₂. The reaction was heated to 40 °C for 4 hours more and then cooled to room temperature. The reaction mixture was treated with 5 N NaOH (1.5 mL) and stirred for 2 hours at room temperature. The reaction was

-143-

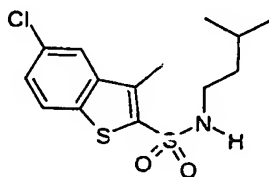
acidified with 1 N HCl (20 mL), diluted with Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.45 g crude product that was purified by preparative HPLC to afford 0.023 g (12%). ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₁H₂₃O₅NCIS₃ 500.0427, found 500.0428.

Example 49

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3-methyl-butyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (3-methyl-butyl)-amide



A solution of 3-methyl-butylamine (0.102 g, 1.17 mmol) and triethylamine (0.118 g, 1.17 mmol) in CH₂Cl₂ (10 mL) was treated with 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (0.300 g, 1.07 mmol) and stirred at room temperature under N₂. The reaction mixture was gravity filtered through a Varian Extube Extraction Column (ChemElut 1005) that had been pre-treated with 4 mL 1 N HCl. The extraction column was washed with CH₂Cl₂ (4X) and the solvent was removed from the filtrate *in vacuo* to afford 0.325 g (92%) that was utilized without further purification. R_f = 0.26 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₄H₁₈ClNO₂S₂ 331, found 332 and 334 (M + 1 and M + 3, 100%).

-144-

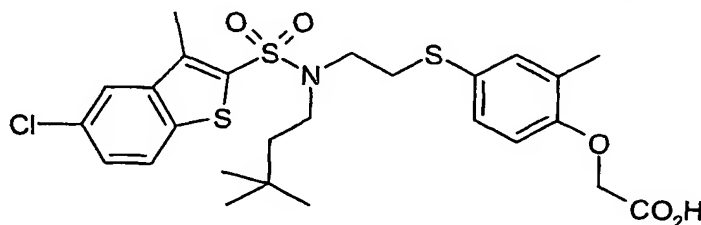
Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3-methyl-butyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

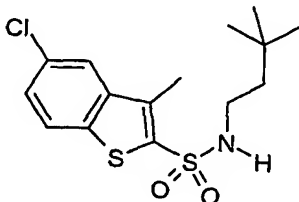
A mixture of [4-(2-chloro-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.160 g, 0.554 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (3-methyl-butyl)-amide (0.183 g, 0.551 mmol) and Cs_2CO_3 (0.234 g, 0.718 mmol) in DMF (7 mL) was stirred at 45 °C for 22 hours. The reaction mixture was cooled and then treated with 5 N NaOH (1.5 mL) and stirred for 4 hours at room temperature. The reaction was acidified with 1 N HCl (20 mL), diluted with Et_2O and then extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.72 g crude product that was purified by preparative HPLC to afford 0.018 g (6%). ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{25}\text{H}_{30}\text{O}_5\text{NCIS}_3\text{Na}$ 578.0872, found 578.0900.

Example 50

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3,3-dimethyl-butyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (3,3-dimethyl-butyl)-amide



Procedure from Example 49, Step A was utilized with 3,3-dimethylbutylamine to afford 0.354 g (96%) that was utilized without further purification. R_f = 0.24 (2/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{15}\text{H}_{20}\text{ClNO}_2\text{S}_2$ 345, found 346 and 348 ($M + 1$ and $M + 3$, 100%).

-145-

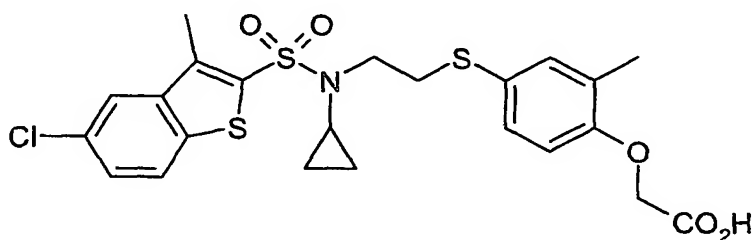
Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(3,3-dimethyl-butyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

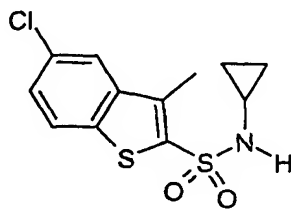
Procedure from Example 49, Step B was utilized to afford 0.62 g crude product that was purified by preparative HPLC to afford 0.032 g (16%) of the title compound. ¹H NMR (400 MHz, CDCl₃); HRMS (ES⁺) *m/z* exact mass calculated for C₂₆H₃₃O₅NCIS₃ 570.1209, found 570.1202.

Example 51

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)cyclopropyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid cyclopropylamide



Procedure from Example 49, Step A was utilized with cyclopropylamine to afford 0.321 g (99%) that was utilized without further purification. *R_f* = 0.16 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₂H₁₂ClNO₂S₂ 301, found 302 and 304 (*M* + 1 and *M* + 3, 100%).

Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)cyclopropyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

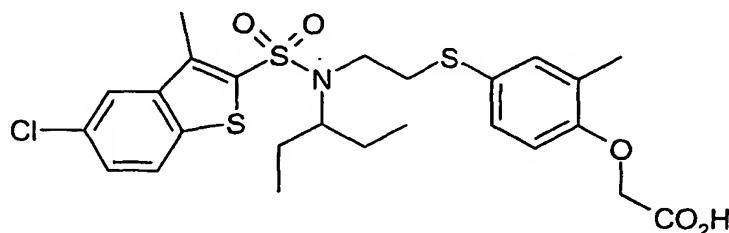
Procedure from Example 49, Step B was utilized to afford 0.38 g crude product that was purified by preparative HPLC to afford 0.027 g (9%) of the title

-146-

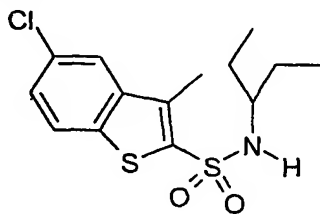
compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{23}\text{H}_{24}\text{O}_5\text{NCIS}_3\text{Na}$ 548.0403, found 548.0403.

Example 52

5 (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(1-ethyl-propyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-ethyl-propyl)-amide



10

Procedure from Example 49, Step A was utilized with 1-ethyl-propylamine to afford 0.343 g (97%) that was utilized without further purification. $R_f = 0.26$ (2/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3): MS (ES^+) m/z mass calculated for $\text{C}_{14}\text{H}_{18}\text{ClINO}_2\text{S}_2$ 331, found 332 and 334 ($M + 1$ and $M + 3$, 100%).

15

Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(1-ethyl-propyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

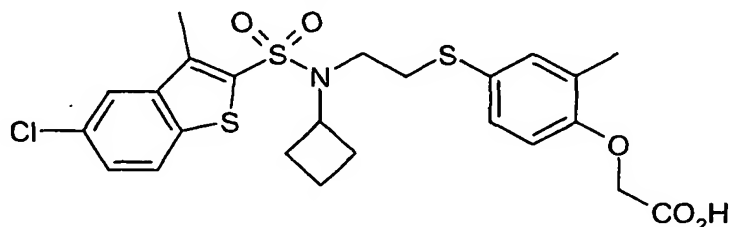
Procedure from Example 49, Step B was utilized to afford 0.007 g (2%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{25}\text{H}_{30}\text{O}_5\text{NCIS}_3\text{Na}$ 578.0872, found 578.0920.

20

-147-

Example 53

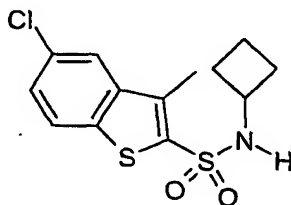
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclobutyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid cyclobutylamide



Procedure from Example 49, Step A was utilized with cyclobutylamine to afford 0.365 g (100%) that was utilized without further purification. $R_f = 0.20$ (2/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{13}\text{H}_{14}\text{ClNO}_2\text{S}_2$ 315, found 316 and 318 ($M + 1$ and $M + 3$, 100%).

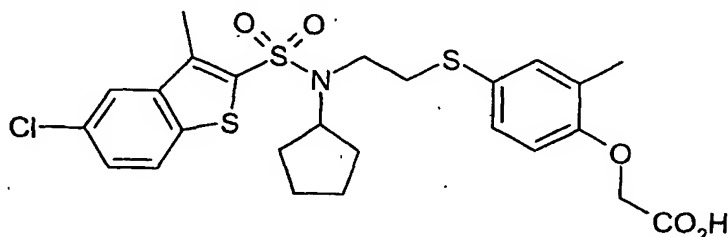
Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclobutyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

15 Procedure from Example 49, Step B was utilized to afford 0.024 g (8%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{24}\text{H}_{26}\text{O}_5\text{NCIS}_3\text{Na}$ 562.0559, found 562.0535.

Example 54

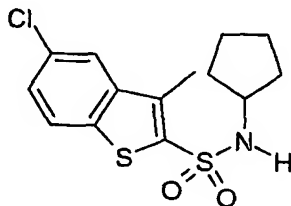
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclopentyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid cyclopentylamide



Procedure from Example 49, Step A was utilized with cyclopentylamine to afford 0.403 g (100%) that was utilized without further purification. $R_f = 0.20$ (2/1 hexanes/acetone). $^1\text{H NMR}$ (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{14}\text{H}_{16}\text{ClNO}_2\text{S}_2$ 329, found 330 and 332 ($M + 1$ and $M + 3$, 100%).

Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclopentyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

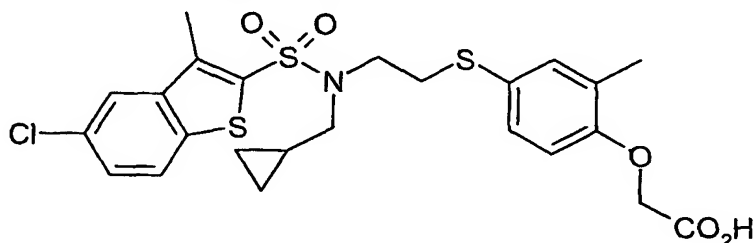
15

Procedure from Example 49, Step B was utilized to afford 0.011 g (4%) of the title compound. $^1\text{H NMR}$ (400 MHz, CDCl_3); MS (ES^-) m/z mass calculated for $\text{C}_{25}\text{H}_{28}\text{O}_5\text{NClS}_3$ 553, found 552 and 554 ($M - 1$ and $M + 1$, 100%).

-149-

Example 55

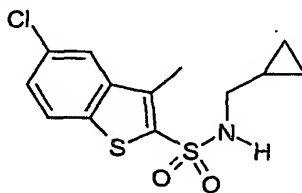
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclopropylmethyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid cyclopropylmethyl-amide



Procedure from Example 49, Step A was utilized with cyclopropylmethylamine to afford 0.333 g (99%) that was utilized without further purification. $R_f = 0.20$ (2/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{13}\text{H}_{14}\text{ClNO}_2\text{S}_2$ 315, found 316 and 318 ($\text{M}+1$ and $\text{M}+3$, 100%).

Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-cyclopropylmethyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

15

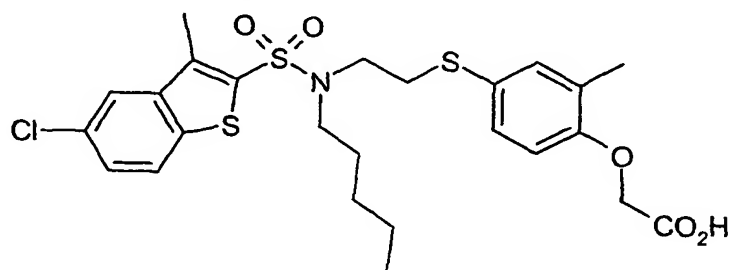
Procedure from Example 49, Step B was utilized to afford 0.332 g crude product that was purified by preparative HPLC to afford 0.020 g (7%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{24}\text{H}_{27}\text{O}_5\text{NCIS}_3$ 540.0740, found 540.0739.

20

-150-

Example 56

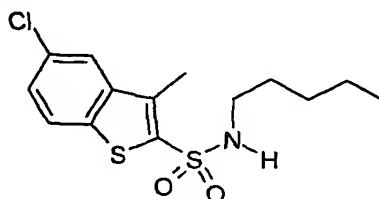
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-pentyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid pentylamide



Procedure from Example 49, Step A was utilized with *n*-pentylamine to afford 0.379 g (100%) that was utilized without further purification. $R_f = 0.22$ (2/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3): MS (ES^+) m/z mass calculated for $\text{C}_{14}\text{H}_{18}\text{ClNO}_2\text{S}_2$ 331, found 332 and 334 ($M + 1$ and $M + 3$, 100%).

Step B

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-pentyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

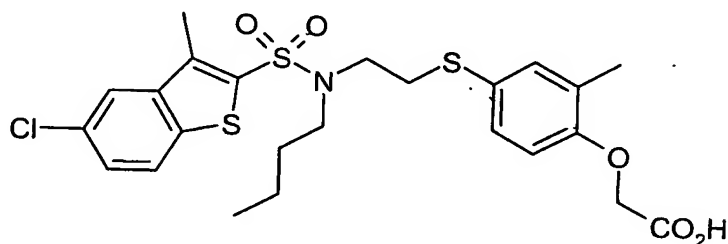
.5

Procedure from Example 49, Step B was utilized to afford 0.045 g (15%) of the title compound. ^1H NMR (400 MHz, CDCl_3): MS (ES^-) m/z exact mass calculated for $\text{C}_{25}\text{H}_{28}\text{O}_5\text{NCIS}_3$ 555, found 554 and 556 ($M - 1$ and $M + 1$, 100%).

-151-

Example 57

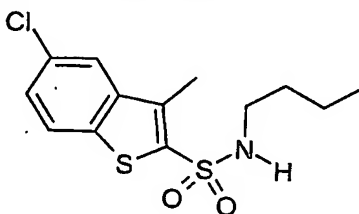
(4-{2-[Butyl-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid butylamide



Procedure from Example 49, Step A was utilized with *n*-butylamine to afford 0.352 g (100%) that was utilized without further purification. $R_f = 0.24$ (2/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{13}\text{H}_{16}\text{ClNO}_2\text{S}_2$ 317, found 318 and 320 ($M + 1$ and $M + 3$, 100%).

10

Step B

(4-{2-[Butyl-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

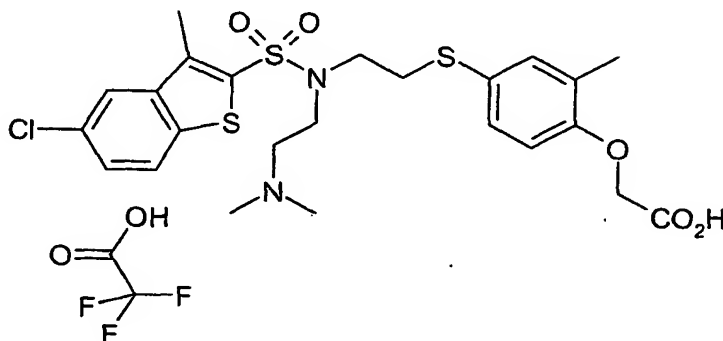
Procedure from Example 49, Step B was utilized to afford 0.030 g (10%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{24}\text{H}_{28}\text{O}_5\text{NCIS}_3\text{Na}$ 564.0716, found 564.0740.

15

-152-

Example 58

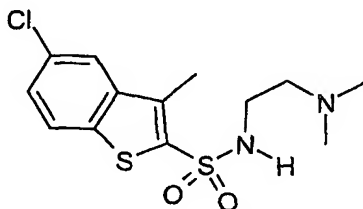
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(2-dimethylamino-ethyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid; trifluoro-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-dimethylamino-ethyl)-amide



A 0 °C solution of N,N-dimethylethylenediamine (0.086 g, 0.976 mmol) and triethylamine (0.134 g, 1.32 mmol) in CH₂Cl₂ (10 mL) was treated with 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (0.250 g, 0.889 mmol) and stirred at room temperature under N₂ until complete by TLC (2/1 hexanes/acetone). The reaction was neutralized with 1 N HCl, diluted with water and then extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.290 g (98%) that was utilized without further purification. R_f = 0.05 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₃H₁₇ClN₂O₂S₂ 332, found 333 and 335 (M + 1 and M + 3, 100%).

Step B

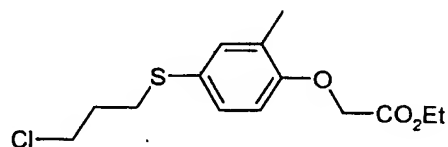
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-(2-dimethylamino-ethyl)-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid; trifluoro-acetic acid (2076995):

20 Procedure from Example 49, Step B was utilized to afford 0.033 g (7%) of the title compound. ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₄H₂₉O₅N₂ClS₃ 556 (free-base), found 557 and 559 (M + 1 and M + 3, 100%).

-153-

Example 59

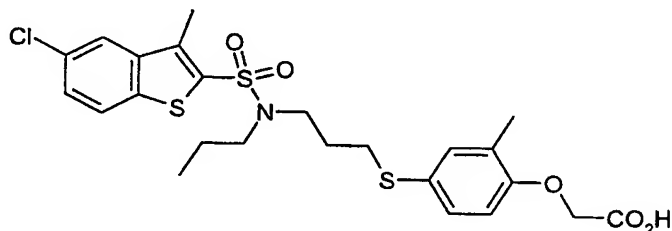
[4-(3-Chloro-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester



A solution of crude (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (5.26 g, 23.2 mmol) in dry DMF (50 mL) was purged with N₂ and then 325 mesh K₂CO₃ (4.82 g, 34.9 mmol) was added and the resultant mixture purged with N₂ for 5 minutes more. 1-Bromo-3-chloropropane (10.98 g, 69.8 mmol) was added dropwise to the reaction which was stirred for 17 hours at room temperature under N₂. The reaction was filtered and the solids washed with Et₂O. The filtrate was acidified with 1 N HCl (70 mL), diluted with Et₂O and then extracted with water (4 X). The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 5/1 hexanes/acetone to afford 5.73 g (82%). R_f = 0.62 (1/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₄H₁₉O₃ClS 302, found 303 and 305 (M + 1 and M + 3, 100%).

Example 60

(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid



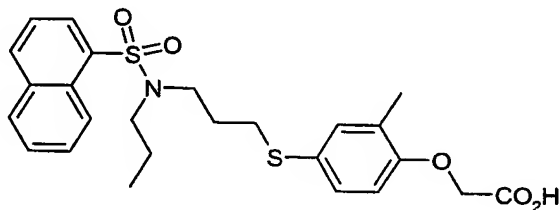
A mixture of [4-(3-chloro-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.100 g, 0.330 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid propylamide (0.100 g, 0.329 mmol) and Cs₂CO₃ (0.140 g, 0.430 mmol) in DMF (7 mL) was stirred at 55 °C for 8 hours. The reaction mixture was cooled and acidified with 1 N HCl (10 mL). The mixture was diluted with water and then extracted with Et₂O. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.183 g crude product that was dissolved in THF (6 mL) and treated with 1 N LiOH (1.6 mL).

-154-

The reaction mixture was stirred for 4 hours at room temperature. The reaction was acidified with 1 N HCl (10 mL), diluted with ethyl acetate and then extracted with water. The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford 0.164 g crude product that was purified by preparative HPLC to afford 0.095 g (53%). ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{24}\text{H}_{28}\text{O}_5\text{NCIS}_3$ 541, found 542 and 544 ($M + 1$ and $M + 3$, 100%).

Example 61

(2-Methyl-4-{3-[(naphthalene-1-sulfonyl)-propyl-amino]-propylsulfanyl}-phenoxy)-acetic acid

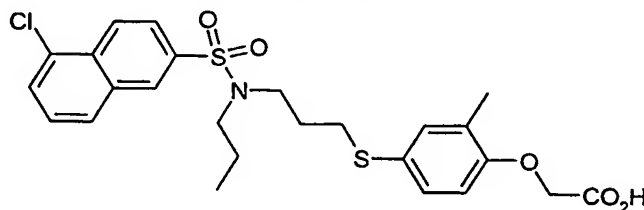


A mixture of [4-(3-chloro-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.108 g, 0.357 mmol), naphthalene-1-sulfonic acid propylamide (0.089 g, 0.357 mmol) and Cs_2CO_3 (0.151 g, 0.463 mmol) in DMF (6 mL) was stirred for 21 hours at 45 $^\circ\text{C}$. The reaction was cooled to room temperature and treated with 5 N NaOH (1.5 mL) and stirred for 2 hours at room temperature. The reaction was acidified with 1 N HCl (20 mL), diluted with Et_2O and then extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.389 g crude product that was purified by preparative HPLC to afford 0.077 g (44%). ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{25}\text{H}_{30}\text{O}_5\text{NS}_2$ 488.1565, found 488.1559.

-155-

Example 62

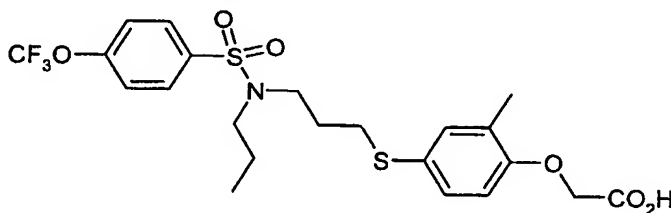
((4-{3-[(5-Chloro-naphthalene-2-sulfonyl)-propyl-amino]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Procedure from Example 61 was utilized to afford 0.076 g (54%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{25}\text{H}_{29}\text{O}_5\text{NS}_2\text{Cl}$ 522.1176, found 522.1213.

Example 63

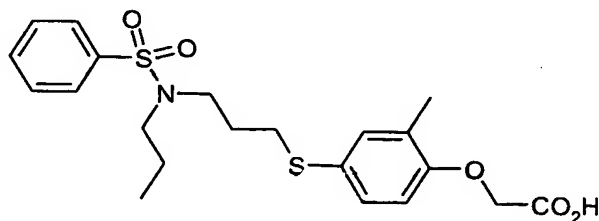
10 (2-Methyl-4-{3-[propyl-(4-trifluoromethoxybenzenesulfonyl)-amino]-propylsulfanyl}-phenoxy)-acetic acid



Procedure from Example 61 was utilized to afford 0.077 g (53%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{22}\text{H}_{27}\text{O}_6\text{NS}_2\text{F}_3$ 522.1232, found 522.1234.

Example 64

{4-[3-(Benzenesulfonyl)-propyl-amino]-propylsulfanyl}-2-methyl-phenoxy}-acetic acid

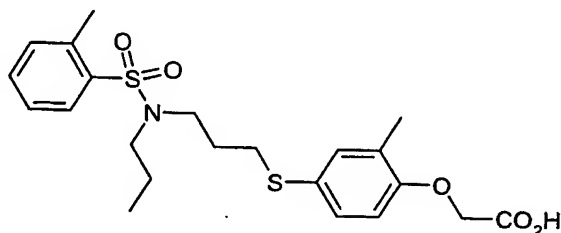


20 Procedure from Example 61 was utilized to afford 0.147 g (65%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{21}\text{H}_{28}\text{O}_5\text{NS}_2$ 438.1409, found 438.1404.

-156-

Example 65

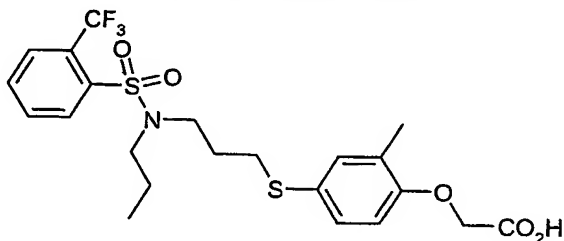
(2-Methyl-4-{3-[propyl-(toluene-2-sulfonyl)-amino]-propylsulfanyl}-phenoxy)-acetic acid



Procedure from Example 61 was utilized to afford 0.126 g (67%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{22}\text{H}_{30}\text{O}_5\text{NS}_2$ 452.1565, found 452.1600.

Example 66

(2-Methyl-4-{3-[propyl-(2-trifluoromethyl-benzenesulfonyl)-amino]-propylsulfanyl}-phenoxy)-acetic acid

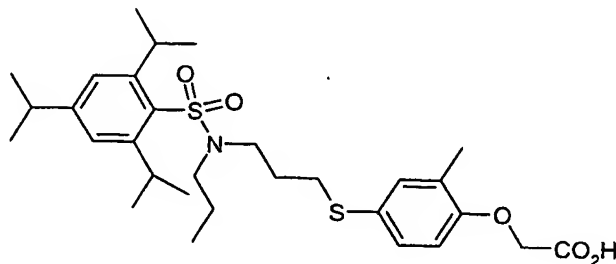


Procedure from Example 61 was utilized to afford 0.070 g (35%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{22}\text{H}_{27}\text{O}_5\text{NS}_2\text{F}_3$ 506.1283, found 506.1288.

-157-

Example 67

(2-Methyl-4-{3-[propyl-(2,4,6-triisopropylbenzenesulfonyl)-amino]-propylsulfanyl}-phenoxy)-acetic acid



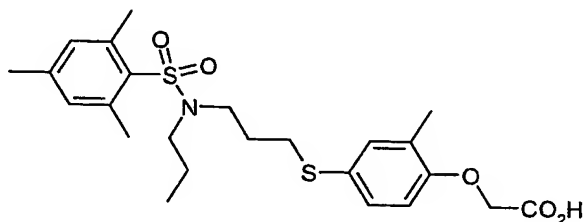
5

Procedure from Example 61 was utilized to afford 0.096 g (55%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{30}\text{H}_{46}\text{O}_5\text{NS}_2$ 564.2817, found 564.2922.

Example 68

10

(2-Methyl-4-{3-[propyl-(2,4,6-trimethyl-benzenesulfonyl)-amino]-propylsulfanyl}-phenoxy)-acetic acid



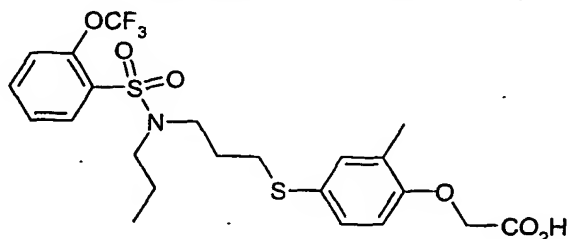
Procedure from Example 61 was utilized to afford 0.111 g (48%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{24}\text{H}_{34}\text{O}_5\text{NS}_2$ 480.1878, found 480.1887.

15

-158-

Example 69

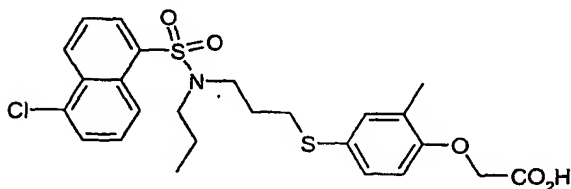
(2-Methyl-4-{3-[propyl-(2-trifluoromethoxybenzenesulfonyl)-amino]-propylsulfanyl}-phenoxy)-acetic acid



5 Procedure from Example 61 was utilized to afford 0.106 g (56%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{22}\text{H}_{27}\text{O}_6\text{NS}_2\text{F}_3$ 522.1232, found 522.1260.

Example 70

10 (4-{3-[(5-Chloro-naphthalene-1-sulfonyl)-propyl-amino]-propylsulfanyl}-2-methylphenoxy)-acetic acid

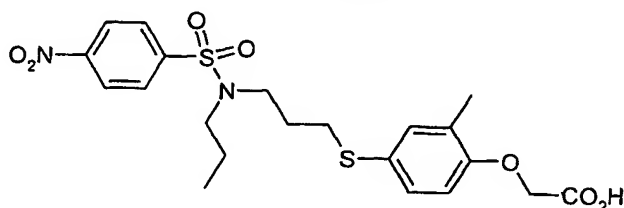


15 Procedure from Example 61 was utilized to afford 0.103 g (56%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{25}\text{H}_{29}\text{O}_5\text{NS}_2\text{Cl}$ 522.1176, found 522.1155.

-159-

Example 71

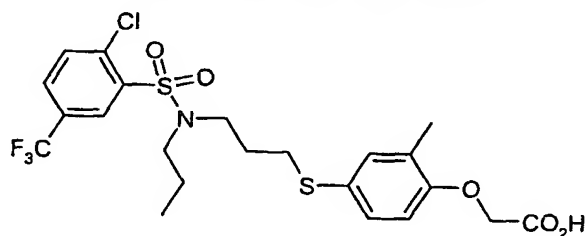
(2-Methyl-4-{3-[(4-nitro-benzenesulfonyl)-propyl-amino]-propylsulfanyl}-phenoxy)-acetic acid



5 Procedure from Example 61 was utilized to afford 0.088 g (39%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{21}\text{H}_{26}\text{O}_7\text{N}_2\text{S}_2\text{Na}$ 505.1079, found 505.1090.

Example 72

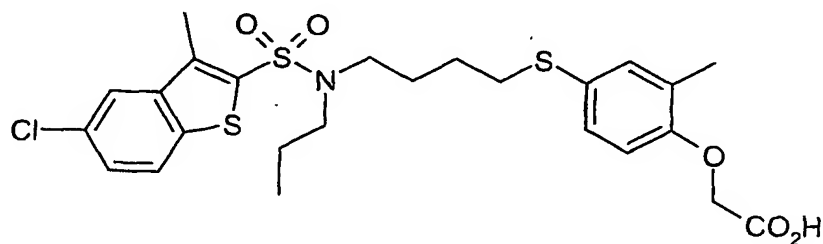
10 ((4-{3-[(2-Chloro-5-trifluoromethyl-benzenesulfonyl)-propyl-amino]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid



15 Procedure from Example 61 was utilized to afford 0.053 g (34%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{22}\text{H}_{26}\text{O}_5\text{N}_2\text{S}_2\text{F}_3\text{Na}$ 562.0712, found 562.0704.

Example 73

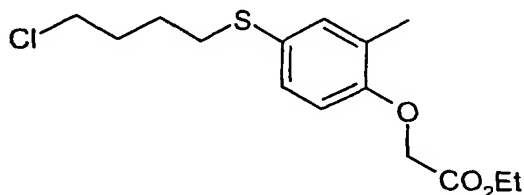
(4-{4-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-butylsulfanyl}-2-methyl-phenoxy)-acetic acid



-160-

Step A

[4-(4-Chloro-butylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester



A solution of crude (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (1.40 g, 6.21 mmol) in dry DMF (15 mL) was purged with N₂ and then 325 mesh K₂CO₃ (1.29 g, 9.33 mmol) was added, and the resultant mixture was purged with N₂ for 5 minutes more. 1-Bromo-4-chlorobutane (3.12 g, 18.2 mmol) was added dropwise to the reaction which was stirred for 17 hours at room temperature under N₂. The reaction was acidified with 1 N HCl (20 mL), diluted with Et₂O and then extracted four times with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 10/1 hexanes/acetone to afford 1.14 g (58%). R_f = 0.31 (2/1 hexanes/acetone). ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₁₅H₂₁O₃ClS 316, found 317 and 319 (M + 1 and M + 3, 100%).

Step B

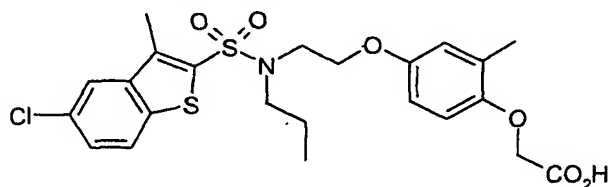
(4-{4-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-butylsulfanyl}-2-methyl-phenoxy)-acetic acid

A mixture of [4-(4-chloro-butylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.102 g, 0.322 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid propylamide (0.098 g, 0.322 mmol) and Cs₂CO₃ (0.136 g, 0.417 mmol) in DMF (7 mL) was stirred at 50 °C for 22 hours. The reaction mixture was cooled and then treated with 5 N NaOH (1.5 mL) and stirred for 4 hours at room temperature. The reaction was acidified with 1 N HCl (20 mL), diluted with Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.464 g crude product that was purified by preparative HPLC to afford 0.068 g (38%) of the title compound. ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₃H₂₃O₃NCIS₃ 555, found 556 and 558 (M + 1 and M + 3, 100%).

-161-

Example 74

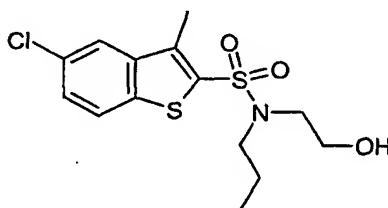
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenoxy)-acetic acid



5

Step A

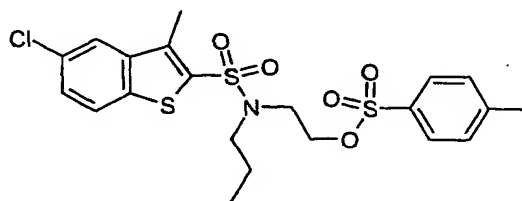
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-ethyl)-propyl-amide



A 0°C solution of 2-(propylamino)ethanol (0.605 g, 5.86 mmol) and triethylamine (1.08 g, 10.7 mmol) in CH₂Cl₂ (25 mL) was treated with 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (1.50 g, 5.33 mmol) and the reaction was warmed to room temperature and stirred for 2 hours under N₂. The reaction was quenched with 1 N HCl (20 mL) and diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 1.82 g (98%) of the title compound. R_f = 0.38 (1/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₁₄H₁₈O₃NS₂Cl 347, found 348 and 350 (M + 1 and M + 3, 100%).

Step B

Toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester



20

A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-ethyl)-propyl-amide (1.82 g, 5.23 mmol), pyridine (1.66 g, 20.9 mmol) and *N,N*-dimethylaminopyridine (0.19 g, 1.55 mmol) in CH₂Cl₂ (50 mL) was treated with *p*-

-162-

toluenesulfonic anhydride (3.42 g, 10.5 mmol), and the reaction stirred at room temperature under N₂ until complete by TLC (2/1 hexanes/acetone). The reaction was quenched with 1 N HCl (30 mL) and diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and purified by column chromatography using a gradient of 9/1 to 4/1 hexanes/acetone to afford 2.76 g (100%) of the title compound. R_f = 0.35 (2/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₂₁H₂₄O₅NS₃Cl 501, found 502 and 504 (M + 1 and M + 3, 100%).

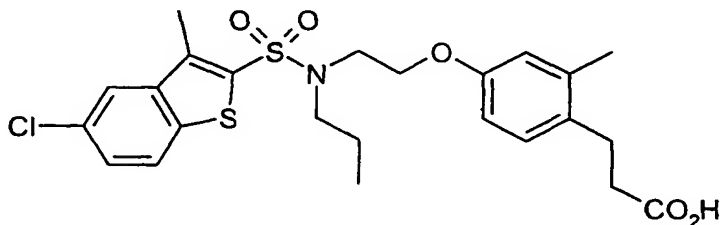
Step C

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenoxy)-acetic acid

A mixture of (4-hydroxy-2-methyl-phenoxy)-acetic acid ethyl ester (0.060g, 0.306 mmol), toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (0.153 g, 0.305 mmol) and Cs₂CO₃ (0.149 g, 0.457 mmol) in dry DMF (7 mL) was stirred at 50 °C for 17 hours under N₂. The reaction was cooled and then treated with 5 N NaOH (2 mL) and stirred at room temperature for 4 hours. The reaction was quenched with 1 N HCl (25 mL), diluted with Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.447 g of crude product that was purified by preparative HPLC to afford 0.087 g (55%) of the title compound. HRMS (ES⁺) *m/z* exact mass calculated for C₂₃H₂₇O₆NCIS₂ 512.0968, found 512.0972.

Example 75

3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenyl)-propionic acid



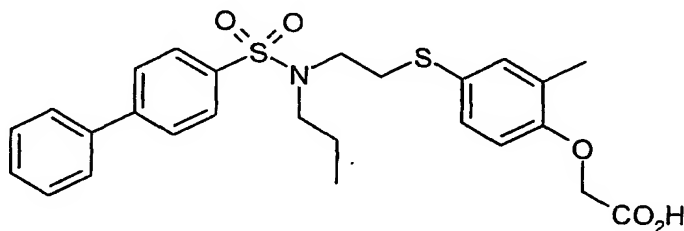
A mixture of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (0.052 g, 0.268 mmol), toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-

-163-

2-sulfonyl)-propyl-amino]-ethyl ester (0.134 g, 0.267 mmol) and Cs_2CO_3 (0.131 g, 0.402 mmol) in dry DMF (7 mL) was stirred at 50 °C for 17 hours under N_2 . The reaction was cooled and then treated with 5 N NaOH (2 mL) and stirred at room temperature for 4 hours. The reaction was quenched with 1 N HCl (25 mL), diluted with Et_2O and then extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.548 g of crude product that was purified by preparative HPLC to afford 0.075 g (55%) of the title compound. ^1H NMR (400 MHz, CDCl_3); HRMS (ES^+) m/z exact mass calculated for $\text{C}_{24}\text{H}_{28}\text{O}_5\text{NCIS}_2\text{Na}$ 532.0995, found 532.1003.

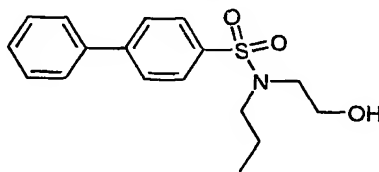
Example 76

(4-{2-[(Biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



Step A

Biphenyl-4-sulfonic acid (2-hydroxy-ethyl)-propyl-amide

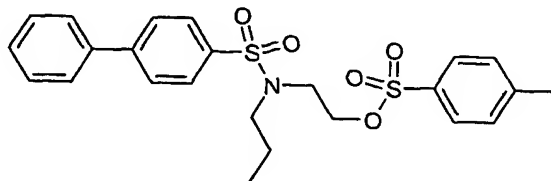


Procedure from Example 74, Step A was utilized with biphenyl-4-sulfonyl chloride to afford 3.34 g (88%) the title compound. $R_f = 0.38$ (1/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $\text{C}_{17}\text{H}_{21}\text{O}_3\text{NS}$ 319, found 320 ($\text{M}+1$, 100%).

-164-

Step B

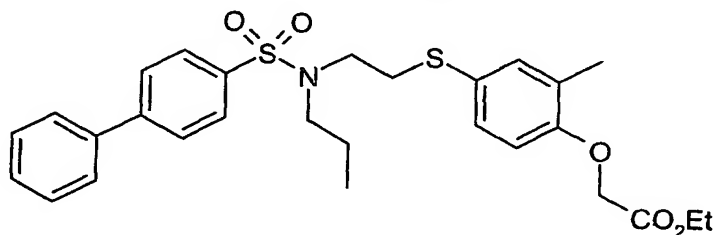
Toluene-4-sulfonic acid 2-[(biphenyl-4-sulfonyl)-propyl-amino]-ethyl ester



5 Procedure from Example 74, Step B was utilized with biphenyl-4-sulfonic acid (2-hydroxy-ethyl)-propyl-amide to afford 2.23 g (45%) of the title compound. $R_f = 0.46$ (1/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $C_{24}H_{27}O_5NS_2$ 473, found 474 ($M + 1$, 100%).

Step C

10 (4-{2-[(Biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.51 g, 2.25 mmol) in dry DMF (8 mL) was purged with N_2 and then Cs_2CO_3 (0.80 g, 2.46 mmol) was added, and the resultant mixture purged with N_2 for 5 minutes more.

15 Toluene-4-sulfonic acid 2-[(biphenyl-4-sulfonyl)-propyl-amino]-ethyl ester (0.53 g, 1.12 mmol) was added to the reaction, which was heated to $50^\circ C$ and stirred for 17 hours under N_2 . The reaction was cooled, acidified with 1 N HCl (20 mL), diluted with Et_2O and then extracted with water. The organic layer was dried (Na_2SO_4), and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and then

20 column purified using 6/1 hexanes/ethyl acetate to afford 0.414 g (70%) of the title compound. $R_f = 0.24$ (2/1 hexanes/ethyl acetate). MS (ES^+) m/z mass calculated for $C_{28}H_{33}O_5NS_2$ 527, found 528 ($M + 1$, 100%).

-165-

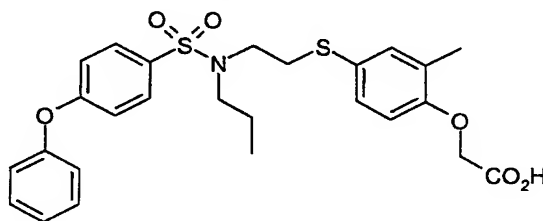
Step D

(4-{2-[(Biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

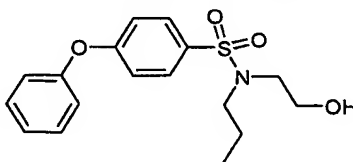
A solution of (4-{2-[(biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (0.414 g, 0.784 mmol) in THF (8 mL) was treated with 1 N LiOH (3.1 mL) and stirred at room temperature for 2.5 hours. The mixture was acidified with 1 N HCl (20 mL) and then diluted with EtOAc and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.450 g (100%) of the title compound. HRMS (ES⁺) *m/z* exact mass calculated for C₂₆H₂₉O₅NS₂Na 522.1385, found 522.1392.

Example 77

(2-Methyl-4-{2-[(4-phenoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Step A

N-(2-Hydroxy-ethyl)-4-phenoxy-N-propyl-benzenesulfonamide

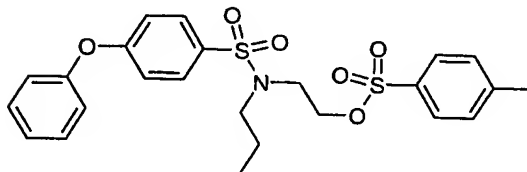


Procedure from Example 74, Step A was utilized with 4-phenoxy-benzenesulfonyl chloride to afford 4.07 g (100%) of the title compound. R_f = 0.33 (1/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₁₇H₂₁O₄NS 335, found 336 (M + 1, 100%).

-166-

Step B

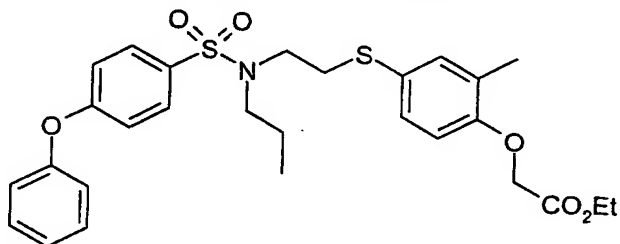
Toluene-4-sulfonic acid 2-[(4-phenoxy-benzenesulfonyl)-propyl-amino]-ethyl ester



Procedure from Example 74, Step B was utilized with *N*-(2-hydroxy-ethyl)-4-phenoxy-*N*-propyl-benzenesulfonamide to afford 5.10 g (86%) of the title compound. $R_f = 0.48$ (1/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $C_{24}H_{27}O_6NS_2$ 489, found 490 ($M + 1$, 100%).

Step C

(2-Methyl-4-{2-[(4-phenoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester



Procedure from Example 76, Step C was utilized with toluene-4-sulfonic acid 2-[(4-phenoxy-benzenesulfonyl)-propyl-amino]-ethyl ester to afford 0.163 g (27%) of the title compound. $R_f = 0.28$ (2/1 hexanes/ethyl acetate). MS (ES^+) m/z mass calculated for $C_{28}H_{33}O_6NS_2$ 543, found 544 ($M + 1$, 100%).

Step D

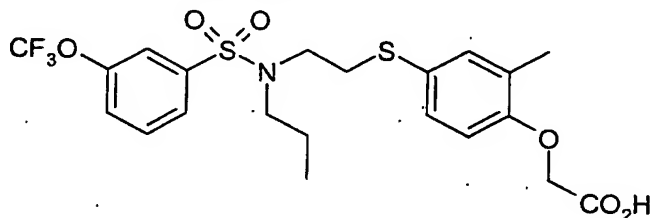
(2-Methyl-4-{2-[(4-phenoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 76. Step D was utilized with (2-methyl-4-{2-[(4-phenoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester to afford 0.131 g (85%) of the title compound. HRMS (ES^+) m/z exact mass calculated for $C_{26}H_{30}O_6NS_2Na$ 516.1515, found 516.1528.

-167-

Example 78

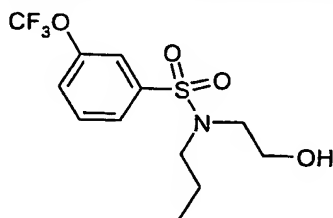
(2-Methyl-4-{2-[propyl-(3-trifluoromethoxybenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



5

Step A

N-(2-Hydroxy-ethyl)-N-propyl-3-trifluoromethoxy-benzenesulfonamide

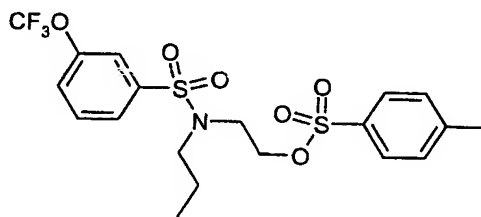


Procedure from Example 74, Step A was utilized with 3-trifluoromethoxy-benzenesulfonyl chloride to afford 1.19 g (95%) of the title compound. $R_f = 0.40$ (1/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $C_{12}H_{16}O_4NSF_3$ 327, found 328 ($M + 1$, 100%).

10

Step B

Toluene-4-sulfonic acid 2-[propyl-(3-trifluoromethoxy-benzenesulfonyl)-amino]-ethyl ester



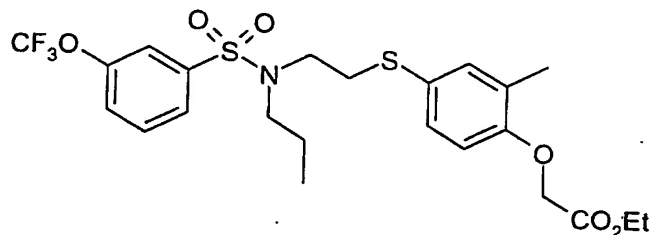
15

Procedure from Example 74, Step B was utilized with *N*-(2-hydroxy-ethyl)-*N*-propyl-3-trifluoromethoxy-benzenesulfonamide to afford 1.56 g (90%) of the title compound. $R_f = 0.48$ (1/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $C_{19}H_{22}O_6NS_2F_3$ 481, found 482 ($M + 1$, 100%).

-168-

Step C

(2-Methyl-4-{2-[propyl-(3-trifluoromethoxybenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester



5 Procedure from Example 76, Step C was utilized with toluene-4-sulfonic acid toluene-4-sulfonic acid 2-[propyl-(3-trifluoromethoxy-benzenesulfonyl)-amino]-ethyl ester to afford 0.425 g (72%) of the title compound. $R_f = 0.26$ (2/1 hexanes/ethyl acetate). MS (ES^+) m/z mass calculated for $C_{23}H_{28}O_6NS_2F_3$ 535, found 536 ($M + 1$, 100%).

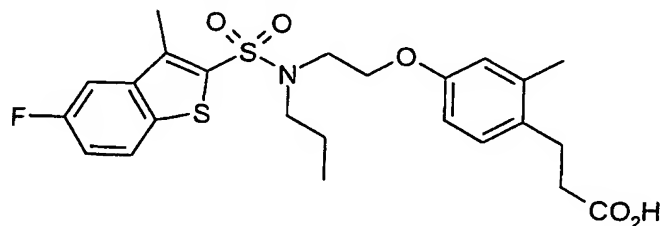
Step D

10 (2-Methyl-4-{2-[propyl-(3-trifluoromethoxybenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Procedure from Example 76, Step D was utilized with (2-methyl-4-{2-[propyl-(3-trifluoromethoxybenzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester to afford 0.438 g (100%) of the title compound. HRMS (ES^+) m/z exact mass calculated for $C_{21}H_{24}O_6NS_2F_3Na$ 530.0895, found 530.0902.

Example 79

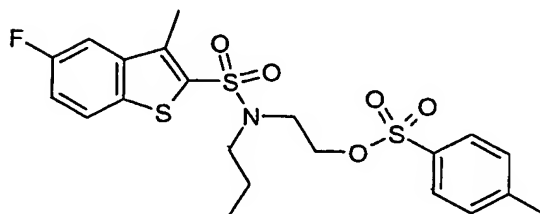
20 3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenyl)-propionic acid



-169-

Step A

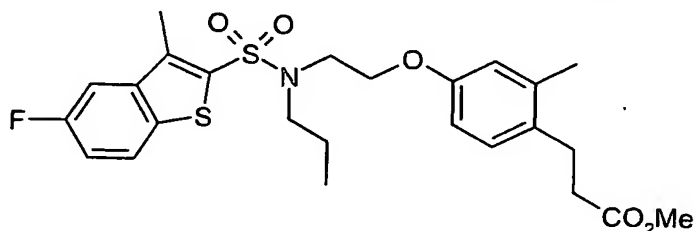
Toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester



5 The procedure for Example 74, Steps A and B were utilized to afford 0.479 g (87%) of the title compound. $R_f = 0.53$ (1/1 hexanes/acetone).

Step B

3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenyl)-propionic acid methyl ester



10

A mixture of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (0.040 g, 0.206 mmol), toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (0.100 g, 0.206 mmol) and Cs_2CO_3 (0.100 g, 0.307 mmol) in dry DMF (10 mL) was stirred at 65 °C for 3 hours under N_2 . The reaction was cooled and quenched with 1 N HCl (10 mL). The mixture was diluted with water and extracted with Et_2O . The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 8/1 hexanes/acetone to afford 0.097 g (92%) of the title compound. $R_f = 0.53$ (1/1 hexanes/acetone). HRMS (ES^+) m/z exact mass calculated for $\text{C}_{25}\text{H}_{30}\text{O}_5\text{NS}_2\text{F}$ 507, found 508 ($\text{M} + 1$, 100%).

15

20

-170-

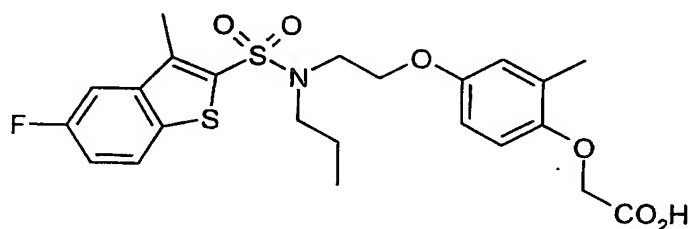
Step C

3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenyl)-propionic acid

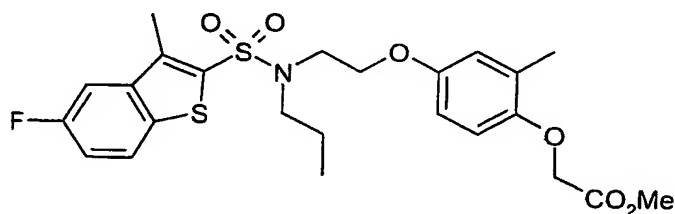
A solution of 3-(4-{2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenyl)-propionic acid methyl ester (0.096, 0.189 mmol) in EtOH (10 mL) was treated with 5 N NaOH (0.5 mL) and heated to reflux for 2 hours. The reaction was cooled and the solvent removed *in vacuo* to afford a residue that was quenched with 1 N HCl (10 mL). The mixture was diluted with water and then extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.077 g (83%) of the title compound. HRMS (ES⁻) *m/z* exact mass calculated for C₂₄H₂₇O₅NS₂F 492.1315, found 492.1317.

Example 80

(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenoxy)-acetic acid

Step A

(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenoxy)-acetic acid methyl ester



A mixture of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (0.050 g, 0.255 mmol), toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (0.115 g, 0.237 mmol) and Cs₂CO₃ (0.116 g, 0.356 mmol) in dry DMF (10 mL) was stirred at 65 °C for 3 hours under N₂. The reaction was cooled and quenched with 1 N HCl (10 mL). The mixture was diluted with water and

-171-

extracted with Et₂O. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 8/1 hexanes/acetone to afford 0.084 g (68%) of the title compound. $R_f = 0.56$ (1/1 hexanes/acetone). MS (ES⁺) m/z mass calculated for C₂₄H₂₈O₆NS₂F 509, found 510 (M+1, 100%).

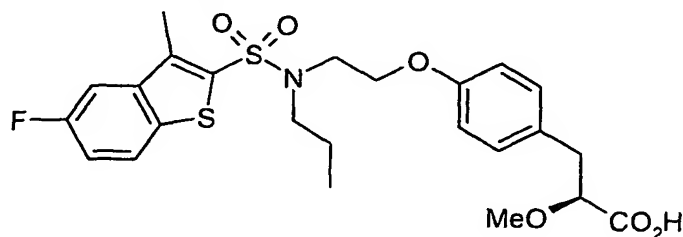
Step B

(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenoxy)-acetic acid

A solution of (4-{2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenoxy)-acetic acid methyl ester (0.084, 0.165 mmol) in EtOH (10 mL) was treated with 5 N NaOH (0.5 mL) and heated to reflux for 2 hours. The reaction was cooled and the solvent was removed *in vacuo* to afford a residue that was quenched with 1 N HCl (10 mL). The mixture was diluted with water and then extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo* to afford 0.072 g (88%) of the title compound. HRMS (ES⁺) m/z exact mass calculated for C₂₃H₂₇O₆NS₂F 496.1264, found 496.1274.

Example 81

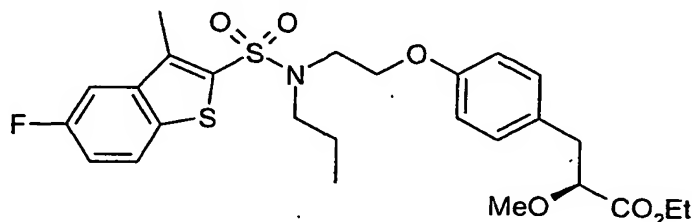
3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-phenyl)-2-methoxy-propionic acid



-172-

Step A

3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-phenyl)-2-methoxy-propionic acid ethyl ester



5 A mixture of 3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (0.037 g, 0.165 mmol), toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (0.080 g, 0.165 mmol) and Cs_2CO_3 (0.080 g, 0.246 mmol) in dry DMF (10 mL) was stirred at 45 °C for 17 hours under N_2 . The reaction was cooled and quenched with 1 N HCl (10 mL). The mixture was diluted with water and
10 extracted with Et_2O . The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 6/1 hexanes/acetone to afford 0.072 g (82%) of the title compound. $R_f = 0.56$ (1/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $\text{C}_{26}\text{H}_{32}\text{O}_6\text{NS}_2\text{F}$ 537, found 538 ($M + 1$, 100%).

Step B

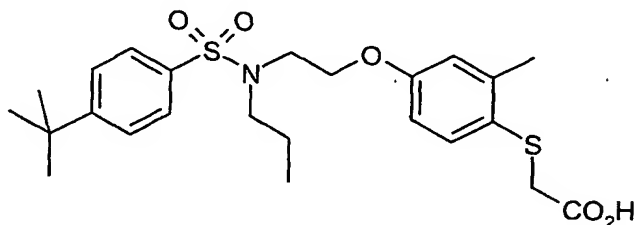
15 3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-phenyl)-2-methoxy-propionic acid

A solution of 3-(4-{2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}phenyl)-2-methoxy-propionic acid ethyl ester (0.072, 0.134 mmol) in EtOH (6 mL) was treated with 5 N NaOH (0.25 mL) and stirred at room
20 temperature for 4 hours. The reaction was cooled and the solvent was removed *in vacuo* to afford a residue that was quenched with 1 N HCl (10 mL). The mixture was diluted with water and then extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.058 g (85%) of the title compound. MS
25 (ES^+) m/z mass calculated for $\text{C}_{24}\text{H}_{28}\text{O}_6\text{NS}_2\text{F}$ 509, found 510 ($M + 1$, 100%).

-173-

Example 82

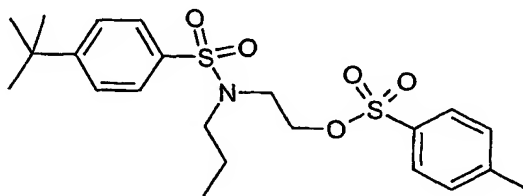
(4-{2-[(4-*tert*-Butyl-benzenesulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenylsulfanyl)-acetic acid



5

Step A

Toluene-4-sulfonic acid 2-[(4-*tert*-butyl-benzenesulfonyl)-propyl-amino]-ethyl ester

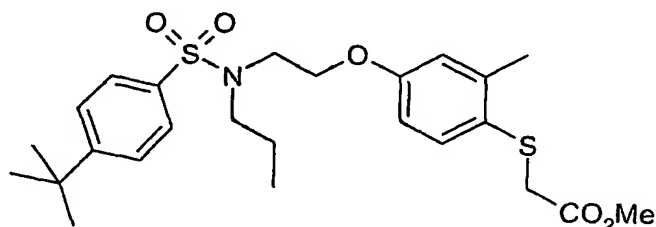


The procedure for Example 74, Steps A and B were utilized to afford 2.81 g (100%) of the title compound. $R_f = 0.57$ (1/1 hexanes/acetone). MS (ES⁺) m/z mass calculated for C₂₂H₃₁O₅NS₂ 453, found 454 (M + 1, 100%).

10

Step B

(4-{2-[(4-*tert*-Butyl-benzenesulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenylsulfanyl)-acetic acid methyl ester



15

A mixture of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.39 g, 1.72 mmol), toluene-4-sulfonic acid 2-[(4-*tert*-butyl-benzenesulfonyl)-propyl-amino]-ethyl ester (0.703 g, 1.55 mmol) and Cs₂CO₃ (0.720 g, 2.21 mmol) in dry DMF (10 mL) was purged with N₂ and then stirred at room temperature for 17 hours and then heated to 50 °C for 1 hour under N₂. The reaction was cooled and acidified with 1 N HCl. The mixture was diluted with water and extracted with Et₂O. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was

20

-174-

absorbed on silica gel and purified by column chromatography using 6/1 hexanes/acetone to afford 0.206 g (26%) of the title compound. $R_f = 0.51$ (1/1 hexanes/acetone).

MS(ES^+) m/z mass calculated for $C_{26}H_{37}O_5NS_2$ 507, found 508 ($M + 1$, 100%).

Step C

- 5 (4-{2-[(4-*tert*-Butyl-benzenesulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenylsulfanyl)-acetic acid

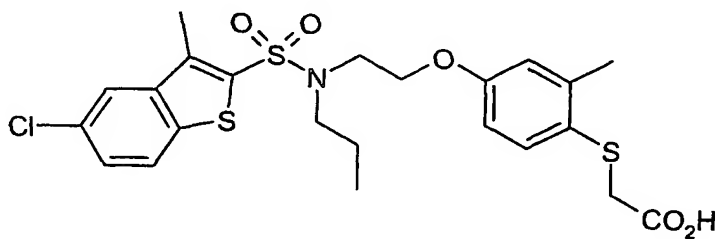
A solution of (4-{2-[(4-*tert*-butyl-benzenesulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenylsulfanyl)-acetic acid methyl ester (0.206, 0.406 mmol) in THF (10 mL) was treated with 1 N LiOH (2 mL) was stirred at room temperature for 2.5 hours.

- 10 The reaction was acidified with 1 N HCl, the mixture was diluted with water, and the mixture extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.210 g (100%) of the title compound. HRMS (ES^+) m/z exact mass calculated for $C_{24}H_{33}O_5NS_2Na$ 502.1698, found 502.1700.

15

Example 83

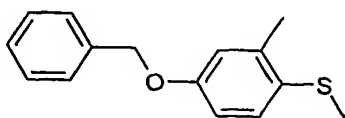
- (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenylsulfanyl)-acetic acid



Step A

20

- 4-benzyloxy-2-methyl-1-methylsulfanyl-benzene



- A mixture of 4-(methylthio)-*m*-cresol (10 g, 64.8 mmol) and 325 mesh K_2CO_3 (11.65 g, 84.3 mmol) in DMF (100 mL) was treated with benzyl bromide (12.22 g, 71.5 mmol) and stirred at room temperature for 17 hr under N_2 . The mixture was
25 filtered using Et_2O to rinse the solids and the filtrate was acidified with 1 N HCl (65 mL). The filtrate was diluted with more Et_2O and then extracted with twice with water and

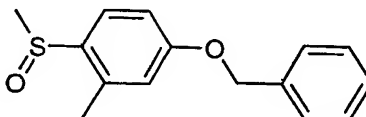
-175-

brine. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 17.03 g (100%) crude title compound, which was carried on without purification. $R_f = 0.66$ (1/1 hexanes/acetone).

Step B

5

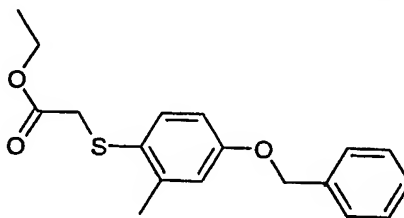
1-Methanesulfinyl-4-benzyloxy-2-methyl-benzene



A 0 °C solution of crude compound obtained in Step A (17.03 g, 64.8 mmol) in chloroform (300 mL) was treated with about 77% *m*-chloroperbenzoic acid (14.53 g, 64.8 mmol) in portions over 10 minutes. The reaction was stirred at 0 °C for 20 minutes and monitored closely by TLC (1/1 hexanes/acetone) until the crude compound (Step A) was gone ($R_f = 0.66$) and the sulfoxide formed ($R_f = 0.27$). The reaction mixture was extracted with saturated NaHCO_3 and then saturated NaHSO_3 . The organic layer was dried (MgSO_4) and the solvent was removed *in vacuo* to afford 18.32 g (100%) crude title compound that was carried on without purification. $R_f = 0.27$ (1/1 hexanes/acetone).

Step C

(4-benzyloxy-2-methyl-phenylsulfanyl)-acetic acid ethyl ester



A solution of crude Step B (18.32 g, 64.8 mmol) in CH_2Cl_2 (250 mL) was treated with trifluoroacetic anhydride (27.2 g, 0.130 mol) and the resultant purple solution was heated to reflux for 30 minutes under N_2 to afford a brown colored solution. The reaction was cooled and the solvent was removed *in vacuo* to give 25.21 g (100%) of Pummerer product that was carried on without purification. $R_f = 0.66$ (1/1 hexanes/acetone).

25

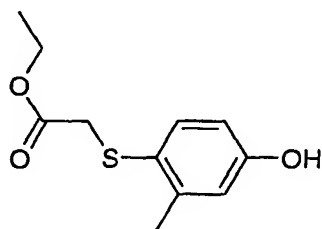
The crude α -trifluoroacetoxy sulfide (25.21 g, assume 64.8 mmol) was combined with bromoethyl acetate (59.02 g, 0.353 mol) in EtOH (230 mL) and purged

-176-

with N₂ for 5 minutes. Potassium carbonate (325 mesh, 32.56 g, 0.236 mol) was added and the reaction mixture stirred for 17 hours at room temperature under N₂. The reaction mixture was filtered using Et₂O to rinse the solids and the filtrate was acidified with 1 N HCl (100 mL). The filtrate was diluted with more Et₂O and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and purified by flash chromatography using 10/1 hexanes/acetone to afford 6.45 g (35%) of the title compound. R_f = 0.43 (2/1 hexanes/acetone).

Step D

(4-Hydroxy-2-methyl-phenylsulfanyl)-acetic acid ethyl ester

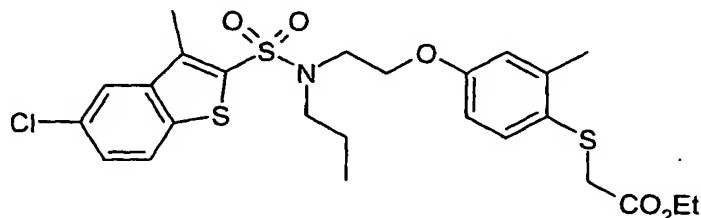


A -78 °C solution of Step C (6.44 g, 20.4 mmol) and dimethylethylsilane (17.96 g, 0.203 mol) in CH₂Cl₂ (150 mL) was treated dropwise with a 1 M solution of TiCl₄ in CH₂Cl₂ (20.4 mL, 20.4 mmol). The reaction mixture was warmed to 0 °C and then room temperature for 3 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and purified by flash chromatography using 98/2 CH₂Cl₂/acetonitrile to afford 2.96 g (64%) of the title compound. R_f = 0.28 (2/1 hexanes/acetone).

-177-

Step E

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenylsulfanyl)-acetic acid ethyl ester



5 A mixture of (4-hydroxy-2-methyl-phenylsulfanyl)-acetic acid ethyl ester (0.090 g, 0.398 mmol), toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (0.219 g, 0.436 mmol) and Cs_2CO_3 (0.194 g, 0.595 mmol) in dry DMF (10 mL) was stirred at 50 °C for 17 hours under N_2 . The reaction was cooled, quenched with 1 N HCl (10 mL), diluted with water and extracted with Et_2O .

10 The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and purified by column chromatography using 6/1 hexanes/acetone afford 0.131 g (59%) of the title compound. $R_f = 0.23$ (2/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $\text{C}_{25}\text{H}_{30}\text{O}_5\text{NCIS}_3$ 555, found 556 and 558 ($M + 1$ and $M + 3$, 100%).

Step F

15 (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenylsulfanyl)-acetic acid

A solution of (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-methyl-phenylsulfanyl)-acetic acid ethyl ester (0.131 g, 0.236 mmol) in THF (8 mL) was treated with 1 N LiOH (1.5 mL) and stirred at room temperature for 4 hours. The reaction was quenched with 1 N HCl (20 mL), diluted with ethyl acetate and then extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.128 g (100%) of the title compound that was further purified by preparative HPLC to afford 0.059 pure title compound (48%).

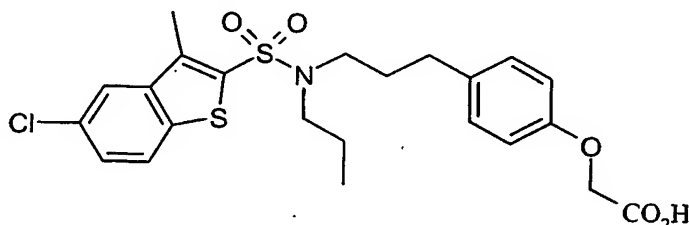
20 MS (ES^-) m/z mass calculated for $\text{C}_{23}\text{H}_{26}\text{O}_5\text{NCIS}_3$ 527, found 526 and 528 ($M-1$ and $M+1$, 100%).

25

-178-

Example 84

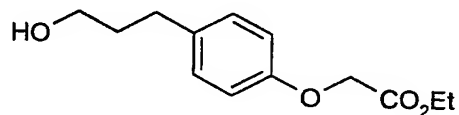
(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-acetic acid



5

Step A

[4-(3-Hydroxy-propyl)-phenoxy]-acetic acid ethyl ester ethyl ester

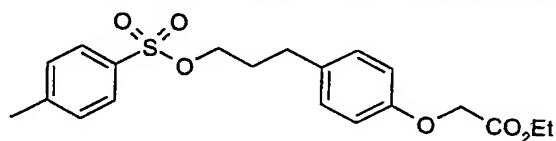


A mixture of 3-(4-hydroxyphenyl)-1-propanol (10.0 g, 65.7 mmol), ethylbromoacetate (32.9 g, 0.197 mol) and 325 mesh K_2CO_3 (13.6 g, 98.4 mmol) in ethanol (150 mL) was heated to reflux for 1.5 hours under N_2 . The reaction was cooled, filtered and the filtrate was quenched with 1 N HCl (100 mL). The filtrate was diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 6/1 hexanes/acetone afford 13.13 g (84%) of the title compound.

$R_f = 0.33$ (1/1 hexanes/acetone).

Step B

{4-[3-(Toluene-4-sulfonyloxy)-propyl]-phenoxy}-acetic acid ethyl ester



A solution of [4-(3-hydroxy-propyl)-phenoxy]-acetic acid ethyl ester ethyl ester (2.00 g, 8.39 mmol), pyridine (2.66 g, 33.6 mmol) and *N,N*-dimethylaminopyridine (0.31 g, 2.54 mmol) in CH_2Cl_2 (75 mL) was treated with *p*-toluenesulfonic anhydride (5.48 g, 16.8 mmol) and the reaction stirred at room temperature under N_2 for 3 hours. The reaction was quenched with 1 N HCl (50 mL) and diluted with more CH_2Cl_2 and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed

-179-

in vacuo to afford crude product that was purified by column chromatography using 6/1 hexanes/acetone to afford 2.78 g (84%) of the title compound. $R_f = 0.47$ (1/1 hexanes/acetone).

5

Step C

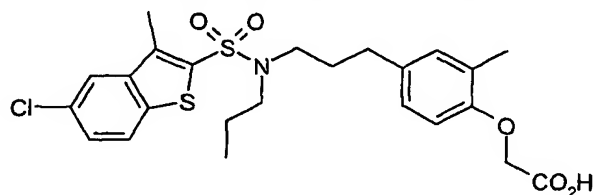
(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-acetic acid

A mixture of {4-[3-(toluene-4-sulfonyloxy)-propyl]-phenoxy}-acetic acid ethyl ester (0.26 g, 0.662 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid propylamide (0.200 g, 0.662 mmol) and Cs_2CO_3 (0.280 g, 0.859 mmol) in DMF (10 mL) was stirred at 50 °C for 4 hours. The reaction mixture was cooled and acidified with 1 HCl (10 mL). The mixture was diluted with water and then extracted with Et_2O . The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product that was dissolved in EtOH (15 mL) and treated with 5 N NaOH (1 mL). The reaction mixture was stirred for 2 hours at room temperature. The solvent was removed *in vacuo* to afford a residue that was acidified with 1 N HCl (10 mL). The mixture was diluted with CH_2Cl_2 and then extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using a gradient of 3/1 hexanes/acetone then 100% acetone to afford 0.070 g (21%) of the title compound. HRMS (ES^+) m/z exact mass calculated for $\text{C}_{23}\text{H}_{27}\text{O}_5\text{NCIS}_2$ 496.1019, found 496.1031.

-180-

Example 85

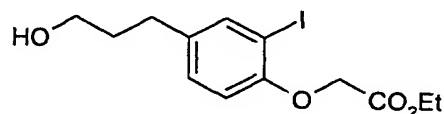
(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-2-methyl-phenoxy)-acetic acid



5

Step A

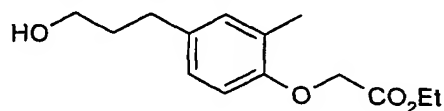
[4-(3-Hydroxy-propyl)-2-iodo-phenoxy]-acetic acid ethyl ester



A mixture of [4-(3-hydroxy-propyl)-phenoxy]-acetic acid ethyl ester ethyl ester (0.50 g, 2.09 mmol), silver sulfate (1.31 g, 4.20 mol) and iodine (1.07 g, 4.22 mmol) in ethanol (10 mL) was stirred at room temperature for 17 hours under N₂. The reaction mixture was filtered the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 3/1 hexanes/acetone afford 0.24 g (31%) of the title compound. R_f = 0.21 (2/1 hexanes/acetone).

Step B

[4-(3-Hydroxy-propyl)-2-methyl-phenoxy]-acetic acid ethyl ester



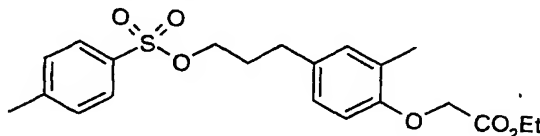
A mixture of [4-(3-hydroxy-propyl)-2-iodo-phenoxy]-acetic acid ethyl ester (0.23 g, 0.632 mmol), methylboronic acid (0.113 g, 1.89 mol) and cesium fluoride (0.34 g, 2.24 mmol) in 1,4-dioxane (4 mL) was stirred at room temperature and purged with N₂ for 3 minutes. The reaction was treated with 1.1' bis(diphenylphosphino) ferrocene palladium (II) chloride, CH₂Cl₂ complex (0.040 g) and then stirred at 80 °C for 1 hour under N₂. The reaction mixture was cooled and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and purified by column chromatography using 3/1 hexanes/acetone afford 0.086 g (54%) of the title compound.

R_f = 0.37 (1/1 hexanes/acetone).

-181-

Step C

{2-Methyl-4-[3-(toluene-4-sulfonyloxy)-propyl]-phenoxy}-acetic acid ethyl ester



A solution of [4-(3-hydroxy-propyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.086 g, 0.341 mmol), pyridine (0.108 g, 1.36 mmol) and *N,N*-dimethyl-aminopyridine (0.012 g, 0.098 mmol) in CH₂Cl₂ (8 mL) was treated with *p*-toluenesulfonic anhydride (0.222 g, 0.680 mmol) and the reaction stirred at room temperature for 1 hour under N₂. The reaction was quenched with 1 N HCl (5 mL) and diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 6/1 hexanes/acetone to afford 0.117 g (84%) of the title compound. *R*_f = 0.49 (1/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₂₁H₂₆O₆S 406, found 424 (M + NH₄).

Step D

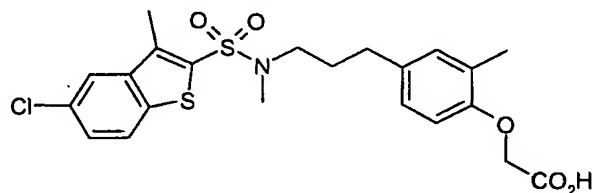
(4-{3-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-propyl}-2-methyl-phenoxy)-acetic acid

A mixture of {2-methyl-4-[3-(toluene-4-sulfonyloxy)-propyl]-phenoxy}-acetic acid ethyl ester (0.117 g, 0.288 mmol), 5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonic acid propylamide (0.087 g, 0.286 mmol) and Cs₂CO₃ (0.122 g, 0.374 mmol) in DMF (8 mL) was stirred at 50 °C for 3 hours. The reaction mixture was cooled and acidified with 1 N HCl (10 mL). The mixture was diluted with water and then extracted with Et₂O. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.495 g of crude product that was dissolved in EtOH (10 mL) and treated with 5 N NaOH (1.5 mL). The reaction mixture was stirred for 2 hours at room temperature. The solvent was removed *in vacuo* to afford a residue that was acidified with 1 N HCl (10 mL). The mixture was diluted with Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.162 g of crude product that was purified by preparative HPLC to afford 0.049 g (33%) of the title compound. HRMS (ES⁺) *m/z* exact mass calculated for C₂₄H₂₉O₅NCIS₂ 510.1176, found 510.1184.

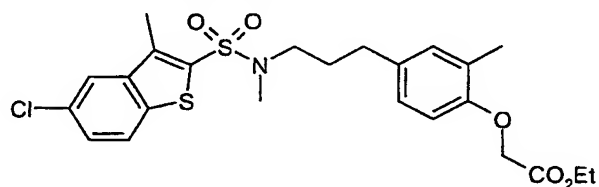
-182-

Example 86

(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-methyl-amino]-propyl}-2-methyl-phenoxy)-acetic acid

Step A

(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-methyl-amino]-propyl}-2-methyl-phenoxy)-acetic acid ethyl ester



A mixture of {2-methyl-4-[3-(toluene-4-sulfonyloxy)-propyl]-phenoxy}-acetic acid ethyl ester (0.120 g, 0.295 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid methylamide (0.081 g, 0.294 mmol) and Cs₂CO₃ (0.125 g, 0.384 mmol) in DMF (8 mL) was stirred at 50 °C for 4 hours. The reaction mixture was cooled and acidified with 1 HCl (3 mL). The mixture was diluted with water and then extracted with Et₂O. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 6/1 hexanes/acetone to afford 0.127 g (85%) of the title compound. *R*_f = 0.54 (1/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₂₄H₂₈O₅NCIS₂ 509, found 510 and 512 (M + 1 and M + 3, 100%).

Step B

(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-methyl-amino]-propyl}-2-methyl-phenoxy)-acetic acid

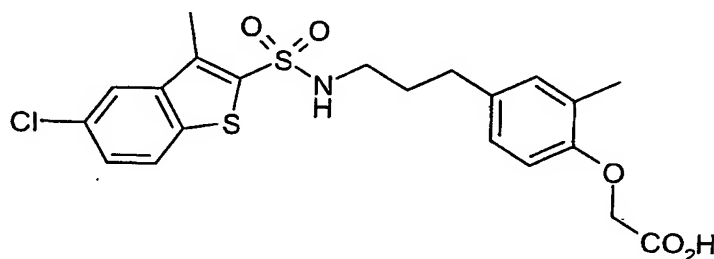
A solution of (4-{3-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-methyl-amino]-propyl}-2-methyl-phenoxy)-acetic acid ethyl ester (0.124 g, 0.243 mmol) in THF (6 mL) and treated with 1 N LiOH (1.2 mL). The reaction mixture was stirred for 2 hours at room temperature. The mixture was acidified with 1 N HCl (10 mL), dilute with water, and extracted with ethyl acetate. The organic layer was dried (Na₂SO₄) and

-183-

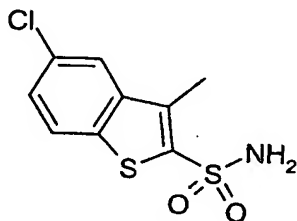
the solvent was removed *in vacuo* to afford 0.118 g (100%) of the title compound.
 HRMS (ES⁺) *m/z* mass calculated for C₂₂H₂₅O₅NCIS₂ 482.0863, found 482.0874.

Example 87

5 {4-[3-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-propyl]-2-methyl-phenoxy}-acetic acid

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid amide



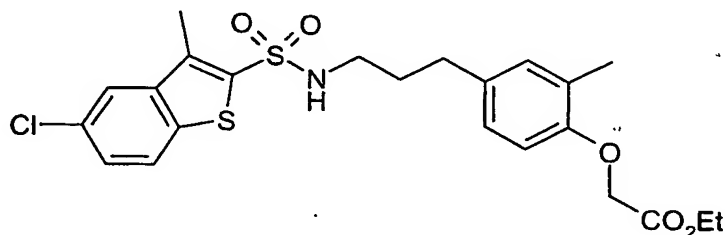
10

A solution of 29% ammonium hydroxide (5 mL) in THF (30 mL) was treated with 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (1.50 g, 5.33 mmol) and stirred at room temperature for 30 minutes under N₂. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried (Na₂SO₄) and
 15 the solvent was removed *in vacuo* to afford 1.37 g (98%) of the title compound that was utilized without further purification. R_f = 0.46 (1/1hexanes/acetone). MS (ES⁻) *m/z* mass calculated for C₉H₈O₂NS₂Cl 261, found 260 and 262 (M-1 and M+1, 100%).

-184-

Step B

{4-[3-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-propyl]-2-methyl-phenoxy}-acetic acid ethyl ester



- 5 A mixture of {2-methyl-4-[3-(toluene-4-sulfonyloxy)-propyl]-phenoxy}-acetic acid ethyl ester (0.259 g, 0.637 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid amide (0.167 g, 0.637 mmol) and Cs_2CO_3 (0.270 g, 0.829 mmol) in DMF (20 mL) was stirred at 50 °C for 17 hours. The reaction mixture was cooled and acidified with 1 HCl (20 mL). The mixture was diluted with water and then extracted with Et_2O .
- 10 The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford 0.495 g of crude product that was purified by column chromatography using a gradient of 8/1 to 4/1 hexanes/acetone to afford 0.129 g (41%). MS (ES^-) m/z mass calculated for $\text{C}_{22}\text{H}_{22}\text{O}_5\text{NCIS}_2$ 495, found 494 and 496 (M-1 and M+1, 100%).

Step C

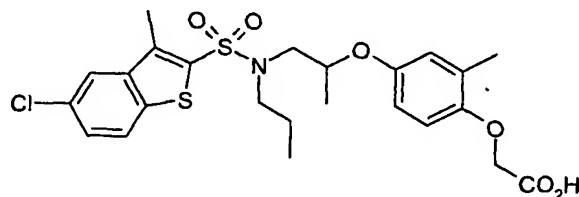
- 15 {4-[3-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-propyl]-2-methyl-phenoxy}-acetic acid

- A solution of (4-{3-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-2-methyl-phenoxy)-acetic acid (0.095 g, 0.192 mmol) in THF (4 mL) and treated with 1 N LiOH (1 mL). The reaction mixture was stirred for 2 hours at
- 20 room temperature. The mixture was acidified with 1 N HCl (6 mL), dilute with water, and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.092 g (100%) of the title compound. MS (ES^+) m/z mass calculated for $\text{C}_{21}\text{H}_{22}\text{O}_5\text{NCIS}_2$ 467, found 468 and 470 (M + 1 and M + 3, 100%).

-185-

Example 88

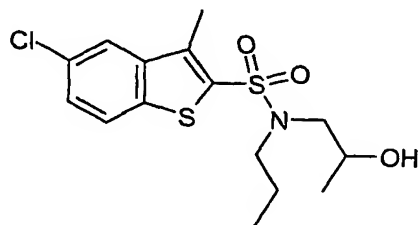
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methylethoxy}-2-methyl-phenoxy)-acetic acid



5

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide



A 0 °C solution of 1-amino-2-propanol (0.59 g, 7.86 mmol) and triethylamine (1.44 g, 14.2 mmol) in CH₂Cl₂ (75 mL) was treated with 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (2.0 g, 7.11 mmol) and the mixture was warmed to room temperature and stirred for 1 hour under N₂. The reaction was quenched with 1 N HCl (20 mL) and diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 2.27 g (100%) of crude 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide that was utilized without purification.

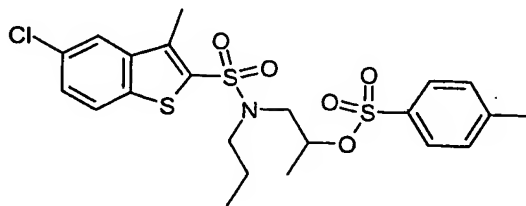
A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide (2.27 g, assume 7.11 mmol) and iodopropane (1.57 g, 9.24 mmol) in DMF (50 mL) was treated with cesium carbonate (3.01 g, 9.24 mmol) and the reaction mixture was stirred at 50 °C for 2.5 hours under N₂. The reaction mixture was cooled and quenched with 1 N HCl (30 mL). The mixture was diluted with more Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was column purified using 4/1 hexanes/acetone to afford 2.48 g (96%) of the title compound. R_f = 0.58 (1/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₁₅H₂₀O₃NS₂Cl 361, found 362 and 364 (M + 1 and M + 3, 100%).

25

-186-

Step B

Toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester



5 A 0 °C solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (2.48 g, 6.85 mmol) pyridine (2.17 g, 27.4 mmol) and *N,N*-dimethylaminopyridine (0.33 g, 2.70 mmol) in CH₂Cl₂ (75 mL) was treated with *p*-toluenesulfonic anhydride (4.47 g, 13.7 mmol), and the mixture was stirred at room temperature under N₂ for 6 hours. The reaction was quenched with 1 N HCl (50 mL) and
10 diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was purified by column chromatography using 9/1 hexanes/acetone to afford 3.59 g (100%) of the title compound. R_f = 0.56 (1/1 hexanes/acetone).

Step C

15 (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid

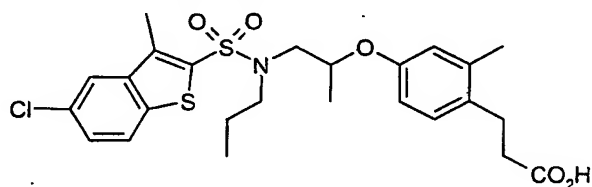
A mixture of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (0.046 g, 0.235 mmol), toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester (0.133 g, 0.258 mmol) and Cs₂CO₃ (0.115
20 g, 0.353 mmol) in DMF (7 mL) was stirred at 60 °C for 20 hours under N₂. The reaction was cooled acidified with 1 N HCl (10 mL), diluted with Et₂O and then extracted twice with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude ester that was dissolved in EtOH (8 mL), treated with 5 N NaOH (1 mL),
25 stirred at 50 °C for 20 minutes and then cooled and stirred at room temperature for 3 hours. The solvent was removed *in vacuo* to give a residue that was acidified with 1 N HCl (10 mL) and then diluted with Et₂O and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.103 g of crude acid that

-187-

was purified by preparative HPLC to afford 0.028 g (22%) of the title compound. HRMS (ES^+) m/z exact mass calculated for $C_{24}H_{29}O_6NCIS_2$ 526.1125, found 526.1113.

Example 89

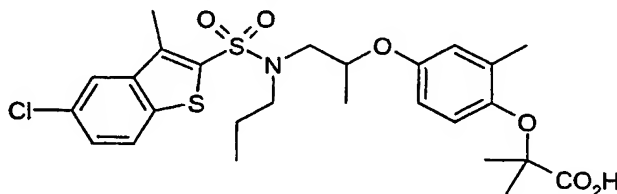
- 5 3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methylethoxy}-2-methyl-phenyl)-propionic acid



- The title compound was prepared by following the procedure of Example 88, Step C utilizing 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester to afford
10 0.032 g (25%). HRMS (ES^+) m/z exact mass calculated for $C_{25}H_{31}O_5NCIS_2$ 524.1332, found 524.1342.

Example 90

- 15 2-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methylethoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

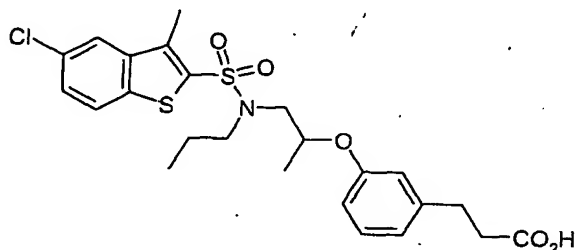


- The title compound was prepared by following the procedure of Example 88, Step C utilizing 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester to afford 0.041 g (28%). HRMS (ES^+) m/z exact mass calculated for $C_{26}H_{33}O_6NCIS_2$
20 554.1438, found 554.1436.

-188-

Example 91

3-(3-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methylethoxy}-phenyl)-propionic acid

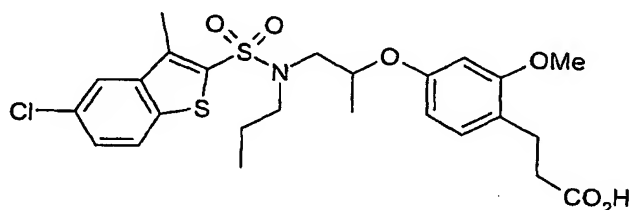


5 The title compound was prepared by following the procedure of Example 88, Step C utilizing 3-(3-hydroxy-phenyl)-propionic acid methyl ester to afford 0.036 g (30%). HRMS (ES⁺) *m/z* exact mass calculated for C₂₄H₂₉O₅NCIS₂ 510.1176, found 510.1181.

10

Example 92

3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methylethoxy}-2-methoxy-phenyl)-propionic acid

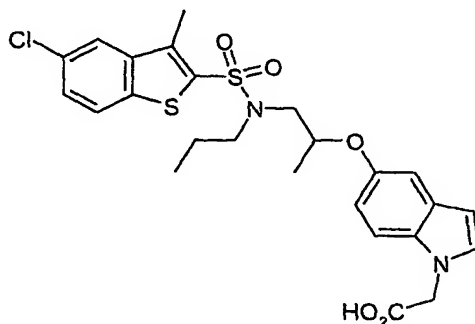


15 The title compound was prepared by following the procedure of Example 88, Step C utilizing 3-(4-hydroxy-2-methoxy-phenyl)-propionic acid ethyl ester to afford 0.028 g (22%). HRMS (ES⁺) *m/z* exact mass calculated for C₂₅H₃₁O₆NCIS₂ 540.1281, found 540.1290.

-189-

Example 93

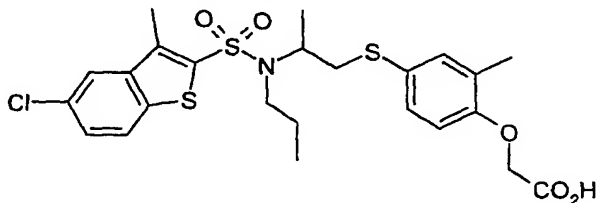
(5-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methylethoxy}-indol-1-yl)-acetic acid



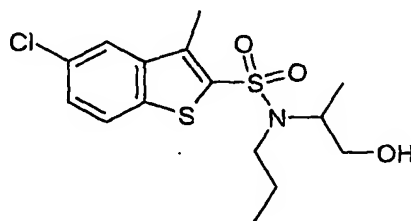
5 The title compound was prepared by following the procedure of Example 88, Step C utilizing (5-hydroxy-indol-1-yl)-acetic acid ethyl ester to afford 0.048 g (33%). ¹H NMR (400 MHz, CDCl₃).

Example 94

10 (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

15 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-1-methyl-ethyl)-propyl-amide



A 0 °C solution of *D,L*-2-amino-1-propanol (0.59 g, 7.86 mmol) and triethylamine (1.44 g, 14.2 mmol) in CH₂Cl₂ (75 mL) was treated with 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (2.0 g, 7.11 mmol), and the mixture was

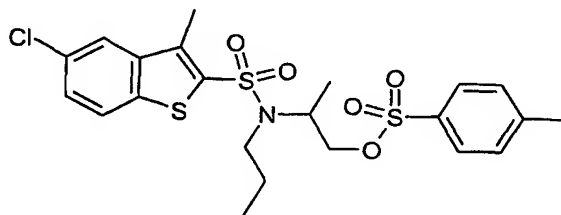
-190-

warmed to room temperature and stirred for 1 hour under N₂. The reaction was quenched with 1 N HCl (30 mL) and diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 2.34 g (100%) of crude 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-1-methyl-ethyl)-amide that was utilized without purification.

A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-1-methyl-ethyl)-amide (2.347 g, assume 7.11 mmol) and iodopropane (1.57 g, 9.24 mmol) in DMF (50 mL) was treated with cesium carbonate (3.01 g, 9.24 mmol) and the reaction mixture was stirred at 50 °C for 2.5 hours under N₂. The reaction mixture was cooled and quenched with 1 N HCl (20 mL). The mixture was diluted with more Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was column purified using 4/1 hexanes/acetone to afford 2.27 g (88%) of the title compound. R_f = 0.45 (1/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₁₅H₂₀O₃NS₂Cl 361, found 362 and 364 (M + 1 and M + 3, 100%).

Step B

Toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl ester



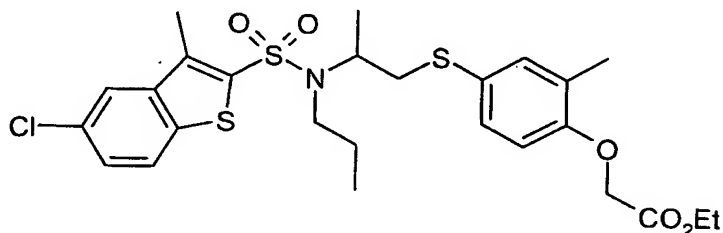
A 0 °C solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-1-methyl-ethyl)-propyl-amide (2.27 g, 6.27 mmol) pyridine (1.98 g, 25.0 mmol) and *N,N*-dimethylaminopyridine (0.23 g, 1.88 mmol) in CH₂Cl₂ (50 mL) was treated with *p*-toluenesulfonic anhydride (4.09 g, 12.5 mmol), and the mixture was stirred at room temperature under N₂ for 1 hour. The reaction was quenched with 1 N HCl (50 mL) and diluted with more CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄), and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and then purified by column chromatography using a gradient of

-191-

9/1 hexanes/acetone then 100% acetone to afford 2.00 g (62%) of the title compound. R_f = 0.51 (1/1 hexanes/acetone).

Step C

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.296 g, 1.31 mmol) in dry DMF (8 mL) was treated with a 60% oil suspension of NaH (0.052 g, 0.130 mmol), and the resultant mixture was stirred at room temperature for 5 minutes under N_2 . The mixture was cooled to 0 °C and then treated dropwise with a solution of toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl ester (0.607 g, 1.17 mmol) in DMF (7 mL). The mixture was stirred at room temperature for 17 hours under N_2 . The reaction was acidified with 1 N HCl (10 mL), diluted with Et_2O and then extracted twice with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude ester that was absorbed on silica gel and column purified using a gradient of 10/1 to 6/1 hexane/acetone to afford 0.403 g (61%) of the title compound. MS (ES^+) m/z mass calculated for $C_{26}H_{32}O_5NCIS_3$ 569, found 570 and 572 ($M + 1$ and $M + 3$, 100%).

Step D

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid

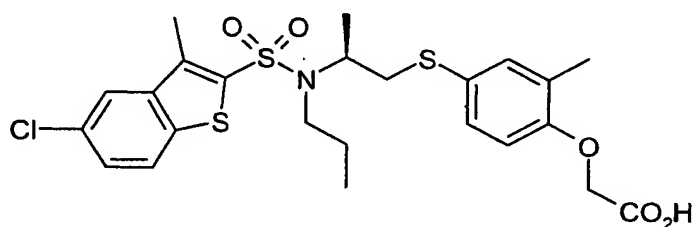
A solution of (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (0.129 g, 0.226 mmol) in EtOH (10 mL) was treated with 5 N NaOH (1.5 mL) and stirred at room temperature until saponification was completed. The solvent was removed *in vacuo* to give a residue that was acidified with 1 N HCl (10 mL) and then diluted with CH_2Cl_2 and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed

-192-

in vacuo to afford 0.114 g (93%) of the title compound. HRMS (ES^+) m/z exact mass calculated for $C_{24}H_{29}O_5NS_3Cl$ 542.0896, found 542.0891.

Example 95

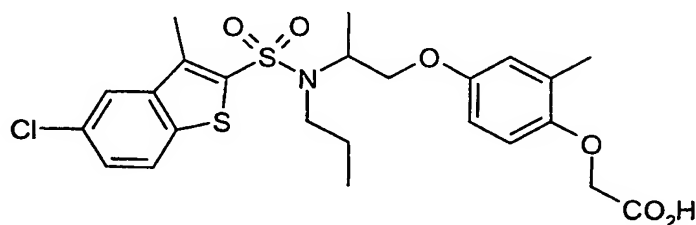
5 (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid (enantiomers 1 and 2)



The compound of (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)propyl-amino]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (Example 94, Step C) was resolved using chiral HPLC (Chiralcel OD 8 x 34 cm, 90/10 heptane/3A EtOH, 370 ml/min, 240 nm UV setting) to give enantiomers of isomer 1 (0.122 g, isomer 1, 100% ee) and isomer 2 (0.106 g, isomer 2, 100% ee). These esters were saponified as described in Example 94, Step D to afford 0.087 g (75%) of the title compound (enantiomer 1) and 0.077 g (76%) of the title compound (enantiomer 2). MS (ES^+) m/z exact mass calculated for $C_{24}H_{29}O_5NS_3Cl$ 541, found 542 and 544 ($M+1$ and $M+3$, 100%).

Example 96

20 (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propoxy}-2-methyl-phenoxy)-acetic acid



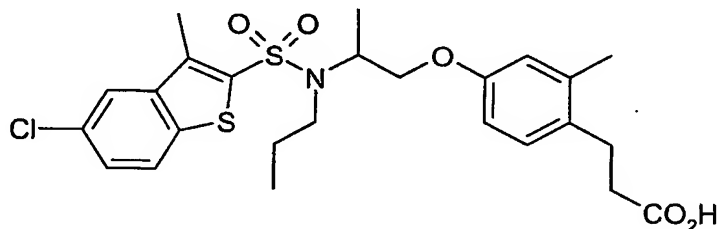
A mixture of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (0.124 g, 0.235 mmol), toluene-4-sulfonic acid toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl ester (0.326 g, 0.632 mmol)

-193-

and Cs_2CO_3 (0.309 g, 0.948 mmol) in DMF (8 mL) was stirred at 55 °C for 20 hours under N_2 . The mixture was cooled, acidified with 1 N HCl (10 mL), diluted with Et_2O and extracted twice with water. The organic layer was dried (Na_2SO_4), and the solvent was removed *in vacuo* to afford 1.12 g of crude ester. The crude ester was dissolved in EtOH (10 mL), treated with 5 N NaOH (1.5 mL) and stirred at 50 °C for 5 minutes, which was then cooled and stirred at room temperature for 2 hours. The solvent was removed *in vacuo* to give a residue that was acidified with 1 N HCl (10 mL) and then diluted with CH_2Cl_2 and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.416 g of crude acid that was purified by preparative HPLC to afford 0.161 g (48%) of the title compound. HRMS (ES^+) m/z exact mass calculated for $\text{C}_{24}\text{H}_{29}\text{O}_6\text{NCIS}_2$ 526.1125, found 526.1124.

Example 97

3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propoxy}-2-methyl-phenyl)-propionic acid

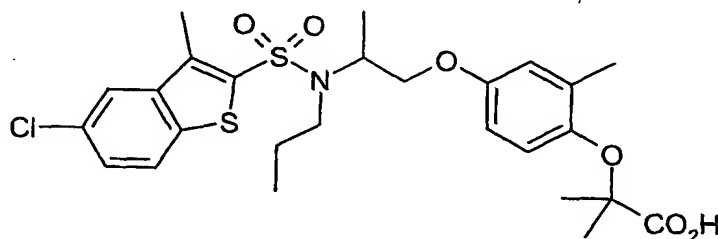


The title compound was prepared by following the procedure as described in Example 96 utilizing 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester to afford 0.112 g (57%). HRMS (ES^+) m/z exact mass calculated for $\text{C}_{25}\text{H}_{31}\text{O}_5\text{NCIS}_2$ 524.1332, found 524.1340.

-194-

Example 98

2-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

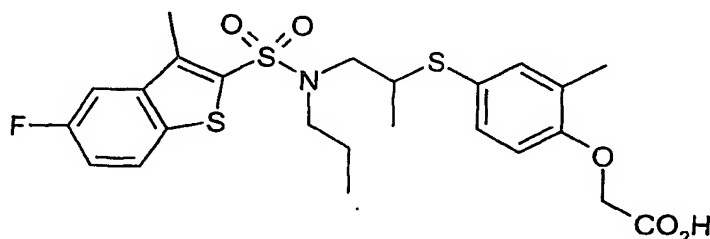


5 The title compound was prepared by following the procedure described in Example 96 utilizing 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester to afford 0.055 g (42%). HRMS (ES⁺) *m/z* exact mass calculated for C₂₆H₃₃O₆NCIS₂ 554.1438, found 554.1444.

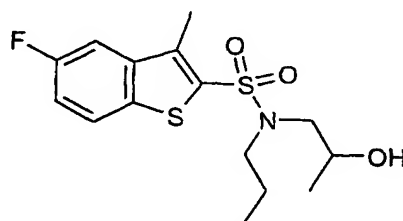
10

Example 99

(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

15 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide



20 A 0 °C solution of 1-amino-2-propanol (0.312 g, 4.15 mmol) and triethylamine (0.76 g, 7.51 mmol) in CH₂Cl₂ (50 mL) was treated with 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (1.0 g, 3.77 mmol), and the mixture was warmed to room temperature and stirred for 1 hour under N₂. The mixture was acidified with 1 N

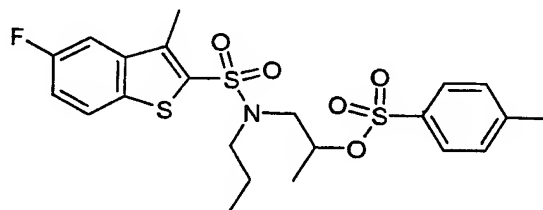
-195-

HCl and diluted with more CH_2Cl_2 and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 1.12 g (98%) of crude 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide that was utilized without purification.

5 A solution of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide (1.12 g, assume 3.69 mmol) and iodopropane (0.835 g, 4.91 mmol) in DMF (40 mL) was treated with cesium carbonate (1.60 g, 4.91 mmol), and the reaction mixture was stirred at 50°C for 2 hours under N_2 . The reaction mixture was cooled and acidified with 1 N HCl (20 mL). The filtrate was diluted with Et_2O and then
10 extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product, which was column purified using 4/1 hexanes/acetone to afford 1.15 g (88%) of the title compound. $R_f = 0.43$ (1/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{NS}_2\text{F}$ 345, found 346 ($\text{M}+1$, 100%).

Step B

15 Toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester



A 0°C solution of 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (0.375 g, 1.13 mmol), pyridine (0.36 g, 4.55 mmol) and
20 *N,N*-dimethylaminopyridine (0.041 g, 0.336 mmol) in CH_2Cl_2 (20 mL) was treated with *p*-toluenesulfonic anhydride (0.74 g, 2.27 mmol), and the mixture was stirred at room temperature under N_2 for 1 hour. The reaction was quenched with 1 N HCl (10 mL) and diluted with more CH_2Cl_2 and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product that was purified
25 by column chromatography using 9/1 hexanes/acetone to afford 0.479 g (87%) of the title compound. $R_f = 0.53$ (1/1 hexanes/acetone). ^1H NMR (400 MHz, CDCl_3). MS (ES^+) m/z mass calcd for $\text{C}_{22}\text{H}_{26}\text{O}_5\text{NS}_3\text{F}$ 499, found 500 ($\text{M} + 1$, 100%).

-196-

Step C

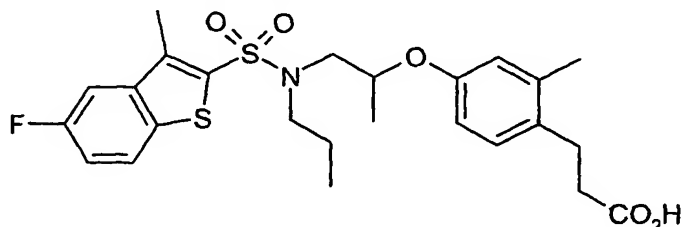
(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester
5 (0.250 g, 1.10 mmol) in dry DMF (8 mL) was treated with a 60% oil suspension of NaH (0.044 g, 1.10 mmol), and the resultant mixture was stirred at room temperature for 5 minutes under N₂. The mixture was cooled to 0 °C and then treated dropwise with a solution of toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester (0.266 g, 0.532 mmol) in DMF (3 mL). The mixture
10 was stirred at room temperature for 17 hours under N₂. The reaction was acidified with 1 N HCl (10 mL), diluted with Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.82 g crude ester. The solid was dissolved in EtOH (15 mL) and treated with 5 N NaOH (1 mL). The solution was then heated and stirred at reflux for 10 minutes. The reaction was cooled, and the
15 solvent was removed *in vacuo* to give a residue. The residue was acidified with 1 N HCl (10 mL), diluted with CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.387 g crude acid, which was purified by preparative HPLC to afford 0.066 g (23%) of the title compound. HRMS (ES⁺) *m/z* exact mass calculated for C₂₄H₂₉O₅NS₃F 526.1192, found 526.1222.

-197-

Example 100

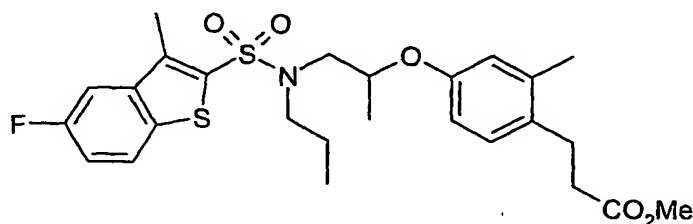
(3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenyl)-propionic acid



5

Step A

3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenyl)-propionic acid methyl ester



A mixture of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (0.048 g, 0.247 mmol), and toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester (Example 79, Step B) (0.133 g, 0.266 mmol) and Cs_2CO_3 (0.121 g, 0.371 mmol) in DMF (8 mL) was stirred at 50 °C for 17 hours under N_2 . The mixture was cooled, acidified with 1 N HCl, diluted with Et_2O and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude ester, which was purified by flash chromatography using 7/1 hexanes/acetone to afford 0.053 g (41%) of the title compound. $R_f = 0.62$ (1/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $\text{C}_{26}\text{H}_{32}\text{O}_5\text{NS}_2\text{F}$ 521, found 522 ($\text{M} + 1$, 100%).

Step B

(3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenyl)-propionic acid

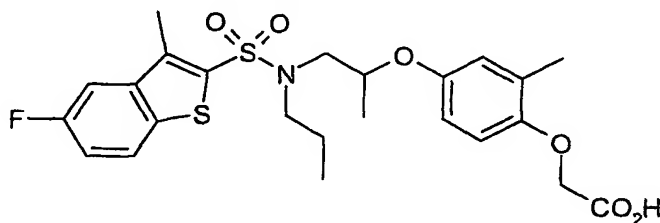
A solution of 3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenyl)-propionic acid methyl ester (0.053 g, 0.102 mmol) in EtOH (8 mL) was treated with 5 N NaOH (0.25 mL), and the mixture was

-198-

stirred at room temperature for 6 hours. The solvent was removed *in vacuo* to give a residue, which was acidified with 1 N HCl, diluted with ethyl acetate and extracted with water. The organic layer was dried (Na₂SO₄), and the solvent was removed *in vacuo* to afford 0.038 g of crude acid that was purified by preparative HPLC to afford 0.023 g (45%) of the title compound. HRMS (ES⁺) *m/z* exact mass calculated for C₂₅H₃₁O₅NS₂F 508.1628, found 508.1624.

Example 101

((4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid

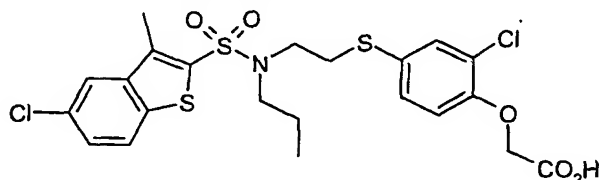


A mixture of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (0.035 g, 0.178 mmol), toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester (Example 99, Step B) (0.097 g, 0.194 mmol) and Cs₂CO₃ (0.089 g, 0.273 mmol) in DMF (6 mL) was stirred at 60 °C for 20 hours under N₂. The mixture was cooled, acidified with 1 N HCl, diluted with Et₂O and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude ester, which was then dissolved in EtOH (8 mL). The solution was treated with 5 N NaOH (1 mL), stirred at 50 °C for 5 minutes, cooled and then stirred at room temperature for 2 hours. The solvent was removed *in vacuo* to give a residue. The residue was acidified with 1 N HCl (10 mL), diluted with CH₂Cl₂ and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.416 g of crude acid, which was purified by preparative HPLC to afford 0.020 g (22%) of the title compound. MS (ES⁺) *m/z* mass calculated for C₂₄H₂₈O₆NS₂F 509, found 510 (M + 1, 100%).

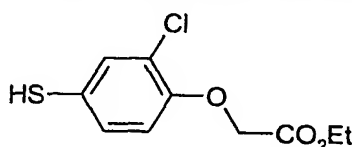
-199-

Example 102

(2-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Step A

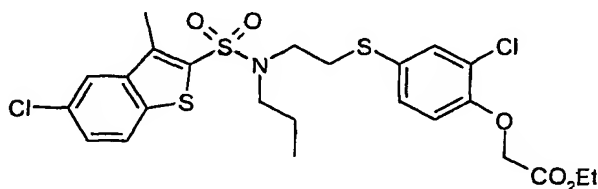
(2-Chloro-4-mercapto-phenoxy)-acetic acid ethyl ester



A mixture of (2-chloro-4-chlorosulfonyl-phenoxy)-acetic acid ethyl ester (1.0 g, 3.19 mmol) and 325 mesh tin powder (1.89 g, 15.9 mmol) in EtOH (5 mL) was treated dropwise with a 4 M solution of HCl in dioxane (5 mL). The reaction mixture was allowed to exotherm and then stirred at reflux for 1.5 hours under N₂. The mixture was cooled to room temperature and the resultant white slurry was filtered through hyflo using CH₂Cl₂ to rinse the solids. The filtrate was washed with water and the organic layer was dried (Na₂SO₄), and the solvent was removed *in vacuo* to afford 0.74 g (95%) of crude product that was utilized without purification. R_f = 0.36 (1/1 hexanes/acetone). MS (ES⁺) *m/z* mass calculated for C₁₀H₁₁O₃SCl 246, found 247 and 249 (M+1 and M+3, 100%).

Step B

(2-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester



A solution of (2-chloro-4-mercapto-phenoxy)-acetic acid ethyl ester (0.34 g, 1.38 mmol) in dry DMF (10 mL) was purged with N₂ and then Cs₂CO₃ (0.584 g, 1.79 mmol) was added. and the resultant mixture was purged with N₂ for 5 minutes more.

-200-

Solid toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (0.55 g, 1.09 mmol) was added to the mixture, which was then stirred for 17 hours at room temperature under N₂. The mixture was acidified with 1 N HCl (20 mL), diluted with Et₂O and then extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and then column purified using 6/1 hexanes/acetone to afford 0.156 g (25%) of the title compound. R_f = 0.59 (1/1 hexanes/EtOAc). MS (ES⁺) *m/z* mass calculated for C₂₄H₂₇O₅NC₂S₃ 575, found 576 and 578 (M+1 and M+3, 100%).

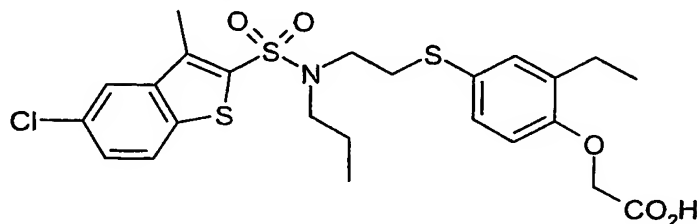
Step C

(2-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

A solution of (2-chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester (0.150 g, 0.260 mmol) in THF (8 mL) was treated with 1 N LiOH (1 mL) and the mixture was stirred at room temperature for 2.5 hours. The mixture was acidified with 1 N HCl, diluted with EtOAc and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.150 g (100%) of the title compound. MS (ES⁺) *m/z* mass calculated for C₂₂H₂₃O₅NC₂S₃ 547, found 548 and 550 (M + 1 and M + 3, 100%).

Example 103

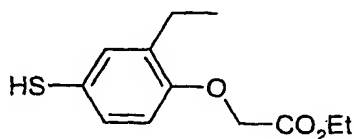
(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-ethyl-phenoxy)-acetic acid



-201-

Step A

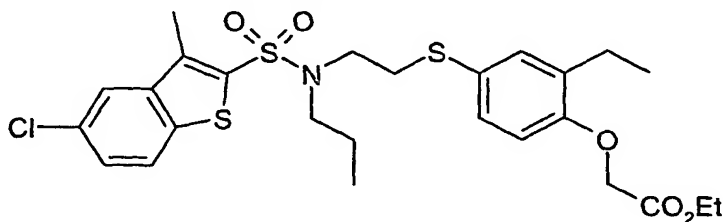
(2-Ethyl-4-mercapto-phenoxy)-acetic acid ethyl ester



A mixture of (4-chlorosulfonyl-2-ethyl-phenoxy)-acetic acid ethyl ester
 5 (1.0 g, 3.25 mmol) and 325 mesh tin powder (1.92 g, 16.3 mmol) in EtOH (5 mL) was
 treated dropwise with a 4 M solution of HCl in dioxane (5 mL). The reaction mixture
 was allowed to exotherm and then stirred at reflux for 1.5 hours under N₂. The reaction
 was cooled to room temperature and the resultant white slurry was filtered through hyflo
 using CH₂Cl₂ to rinse the solids. The filtrate was washed with water and the organic
 10 layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.85 g (100%)
 of crude product that was utilized without purification. MS (ES⁺) *m/z* mass calculated for
 C₁₂H₁₆O₃S 240, found 241 and 243 (M + 1 and M + 3, 100%).

Step B

15 (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-
 2-ethyl-phenoxy)-acetic acid ethyl ester



A solution of (2-ethyl-4-mercapto-phenoxy)-acetic acid ethyl ester (0.30 g,
 1.25 mmol) in dry DMF (7 mL) was purged with N₂ and then Cs₂CO₃ (0.53 g, 1.63
 mmol) was added, and the resultant mixture was purged with N₂ for 5 minutes more.
 20 Solid toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-
 propyl-amino]-ethyl ester (0.313 g, 0.623 mmol) was added to the reaction mixture,
 which was heated to 50 °C and stirred for 3.5 hours under N₂. The reaction was cooled,
 acidified with 1 N HCl (20 mL), diluted with Et₂O and extracted with water. The organic
 layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford crude product,
 25 which was absorbed on silica gel and then column purified using 6/1 hexanes/acetone to
 afford 0.371 g (100%) of partially purified title compound. R_f = 0.67 (1/1

-202-

hexanes/acetone). MS (ES^+) m/z mass calculated for $C_{26}H_{32}O_5NCIS_3$ 569, found 570 and 572 ($M + 1$ and $M + 3$, 100%).

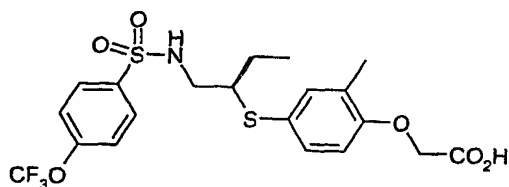
Step C

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-
2-ethyl-phenoxy)-acetic acid

A solution of (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-ethyl-phenoxy)-acetic acid ethyl ester (0.371 g, assume 0.262 mmol) in THF (10 mL) was treated with 1 N LiOH (2.5 mL), and the mixture was stirred at room temperature for 2.5 hours. The mixture was acidified with 1 N HCl, diluted with EtOAc and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 0.391 g crude acid, which was purified by preparative HPLC to afford 0.217 g (64%) of the title compound. HRMS (ES^+) m/z exact mass calculated for $C_{24}H_{28}O_5NCIS_3Na$ 564.0716, found 564.0709.

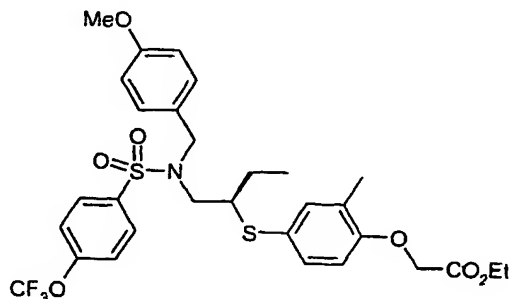
Example 104

(2-Methyl-4-{1-[(4-trifluoromethoxy-benzenesulfonylamino)-methyl]-propylsulfanyl}-phenoxy)-acetic acid



Step A

{4-[1-[(4-Methoxy-benzyl)-(4-trifluoromethoxy-benzenesulfonyl)-amino]-methyl]-propylsulfanyl}-2-methyl-phenoxy]-acetic acid ethyl ester



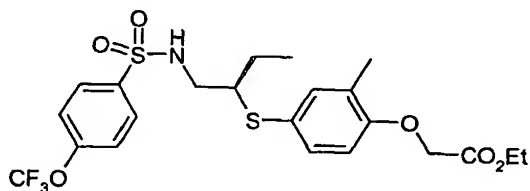
A $0^\circ C$ solution of (4-{1-[(4-Methoxy-benzylamino)-methyl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester trifluoro-acetic acid salt (6.14

-203-

g, 9.70 mmol) in CH_2Cl_2 (150 mL) was treated dropwise with triethylamine (7.84 g, 77.5 mmol) and then 4-(trifluoromethoxy)benzenesulfonyl chloride (3.07 g, 11.8 mmol). The reaction mixture was warmed to room temperature and stirred for 1 hour under N_2 . The reaction was quenched with 1 N HCl (100 mL), diluted with water and extracted with CH_2Cl_2 . The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product that was absorbed on silica gel and column purified with 8/1 hexanes/acetone to afford 3.17 g (51%) of the title compound. $R_f = 0.20$ (2/1 hexanes/acetone). MS (ES^+) m/z mass calculated for $\text{C}_{30}\text{H}_{34}\text{NO}_7\text{S}_2\text{F}_3$ 641, found 642 ($M+1$, 100%).

Step B

(2-Methyl-4-{1-[(4-trifluoromethoxy-benzenesulfonylamino)-methyl]-propylsulfanyl}-phenoxy)-acetic acid ethyl ester



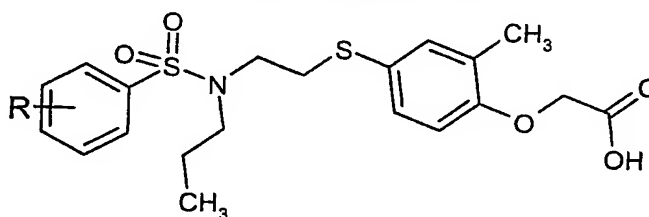
A mixture of [4-(1-{[(4-methoxy-benzyl)-(4-trifluoromethoxy-benzenesulfonyl)-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (3.17 g, 4.94 mmol) and triethylsilane (11.5 g, 98.9 mmol) was treated with trifluoroacetic acid (50 mL), and the mixture was stirred at room temperature for 3 hours under N_2 . The solvent was removed *in vacuo* to afford a residue, which was diluted with Et_2O and extracted with water. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude product, which was absorbed on silica gel and column purified with 99/1 CH_2Cl_2 /acetonitrile to afford 1.13 g (44%) of the title compound. $R_f = 0.56$ (98/2 CH_2Cl_2 /acetonitrile). MS (ES^-) m/z mass calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_6\text{S}_2\text{F}_3$ 521, found 520 ($M - 1$, 100%).

-204-

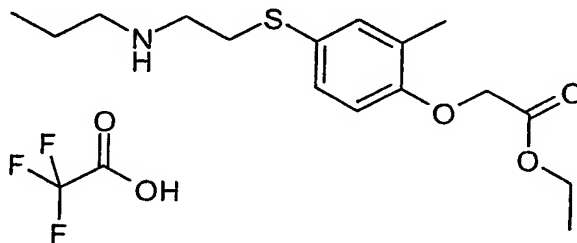
Step C

(2-Methyl-4-{1-[(4-trifluoromethoxy-benzenesulfonylamino)-methyl]-propylsulfanyl}-phenoxy)-acetic acid

A solution of (2-methyl-4-{1-[(4-trifluoromethoxy-benzenesulfonylamino)-methyl]-propylsulfanyl}-phenoxy)-acetic acid ethyl ester (0.050 g, 0.096 mmol) in EtOH (6 mL) was treated with 5 N NaOH (0.5 mL), and the mixture was stirred at room temperature for 2.5 hours. The solvent was removed *in vacuo* to give a residue, which was acidified with 1 N HCl (10 mL), diluted with ethyl acetate and extracted with water. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo* to afford 0.043 g (91%) of the title compound. HRMS (ES⁺) *m/z* exact mass calculated for C₂₀H₂₂NO₆S₂F₃Na 516.0738, found 516.0731.

Example 105General Procedure (1)Step A

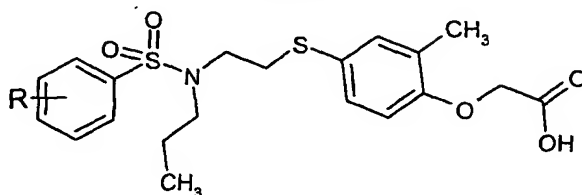
[2-Methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester; compound with trifluoroacetic acid



Trifluoroacetic acid (25.0 ml) was added dropwise to a mixture of ({4-[2-(*tert*-butoxycarbonyl-propyl-amino)-ethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (Example 24, Step C) (5.10 g, 12.4 mmol) and dimethylethyl silane in methylene chloride (100 ml) at room temperature. The mixture was stirred for 2 hours, and the

-205-

solvents were evaporated on a rotavapor to give the title compound, which was used for the next step directly without purification.

Step B

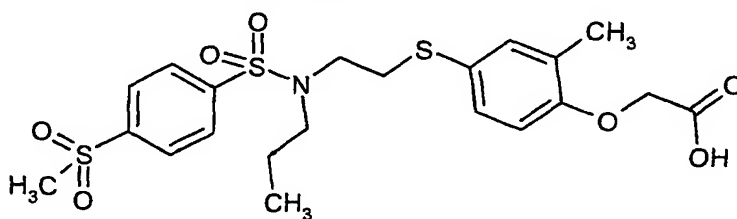
5 Trifluoroacetic acid salt of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (Step A) (0.300 mmol) was added to a mixture of substituted benzene sulfonyl chloride (0.300 mmole) and Et₃N in methylene chloride (2.00 ml). After shaking or standing the reaction at room temperature overnight, the solvents were removed *in vacuo*. The resulting product was purified by column
10 chromatography by eluting with ethyl acetate: hexane (1:4 to 1:2). Evaporation of the solvent afforded the sulfonamide as an ethyl ester. The ethyl ester was then dissolved in THF/MeOH (1:1, 2 ml) and 5.0N NaOH (1.0 ml) was added and let stand at room temperature overnight. The organic solvents were evaporated *in vacuo* and adjusted to pH 2 to 3 with concentrated HCl. The water was removed using ChemElut CE1005. The
15 ChemElut tube was washed with ethyl acetate (40 ml) and the solution was concentrated to dryness. Purification by preparative HPLC (UV-2), eluting with 0.1% TFA in acetonitrile and lyophilization afforded the title compound.

The following Examples 106-137 were prepared by following the General Procedure (1) as described above by using the appropriate starting material.

20

Example 106

(4-{2-[(4-Methanesulfonyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

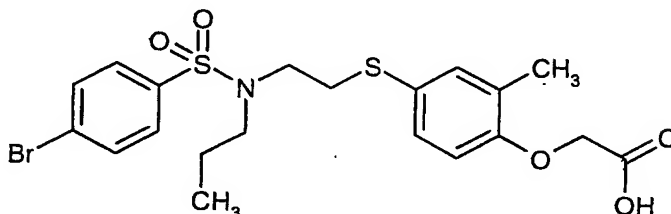


25 MS (ES): 500 (M-H)⁻.

-206-

Example 107

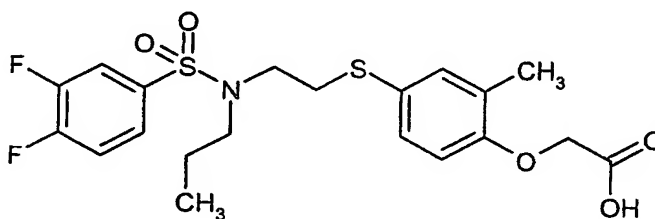
(4-{2-[(4-Bromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass found: 502

Example 108

(4-{2-[(3,4-Difluoro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

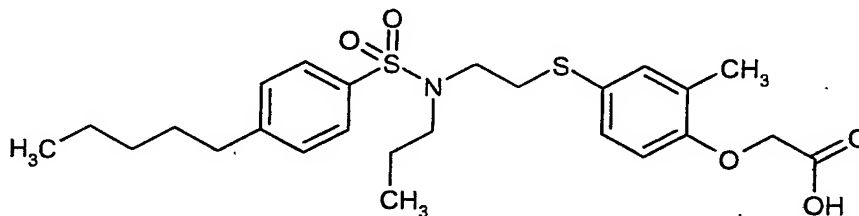


10

Mass found: 459

Example 109

(2-Methyl-4-{2-[(4-pentyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid



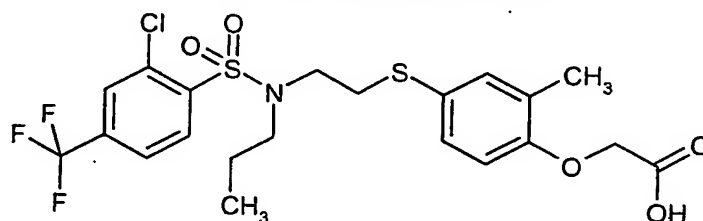
15

Mass found: 493

-207-

Example 110

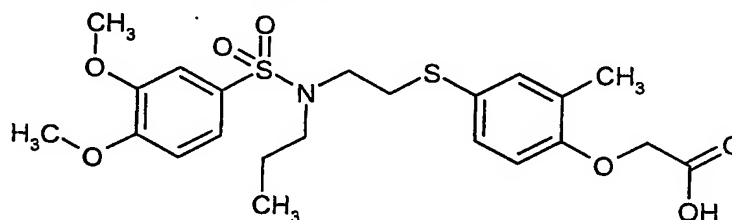
(4-{2-[(2-Chloro-4-trifluoromethyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass found: 526

Example 111

(4-{2-[(3,4-Dimethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

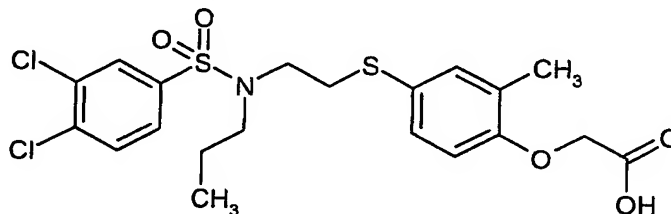


10

Mass found: 483

Example 112

(4-{2-[(3,4-Dichloro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



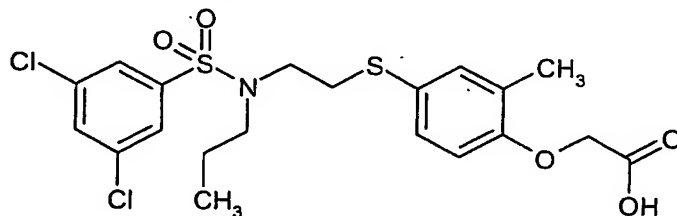
15

Mass found: 492

-208-

Example 113

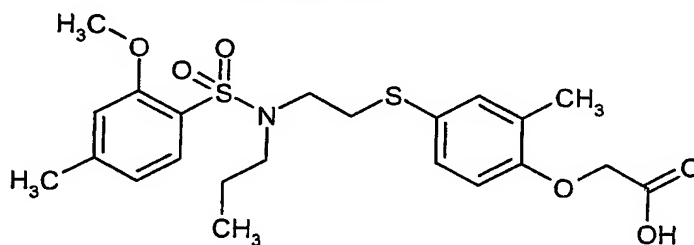
(4-{2-[(3,5-Dichloro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass found: 492

Example 114

(4-{2-[(2-Methoxy-4-methyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



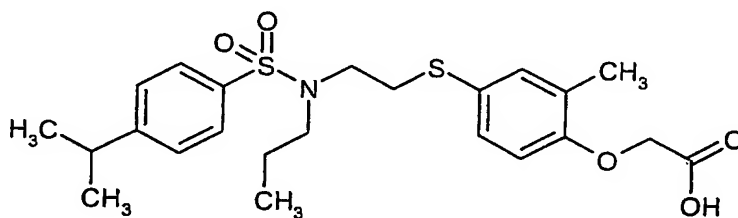
10

Mass found: 467

Example 115

(4-{2-[(4-Isopropyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

15

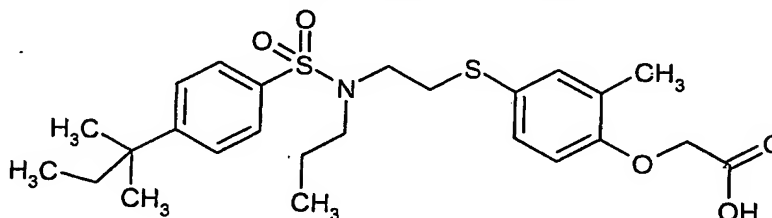


Mass found: 465

-209-

Example 116

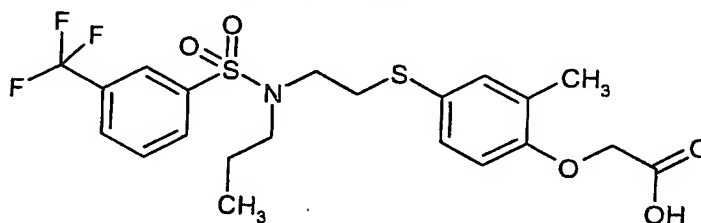
[4-(2-{[4-(1,1-Dimethyl-propyl)-benzenesulfonyl]-propyl-amino}-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid



5 Mass found: 493

Example 117

(2-Methyl-4-{2-[propyl-(3-trifluoromethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

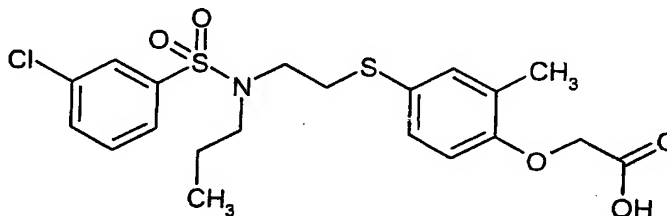


10

Mass spectrum (ES): 492 (M+H)⁺, 490 (M-H)⁻.

Example 118

(4-{2-[(3-Chloro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



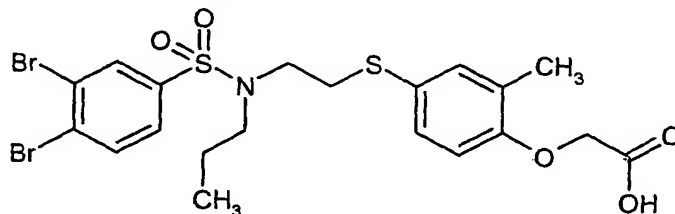
15

Mass spectrum (ES): 458 (M+H)⁺, 456 (M-H)⁻.

-210-

Example 119

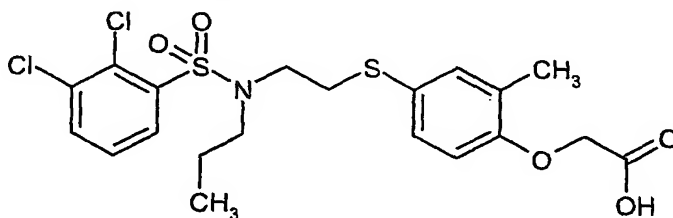
(4-{2-[(3,4-Dibromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid



5 Mass spectrum (ES): 580, 582 (M+H)⁺, 578, 580 (M-H)⁻.

Example 120

(4-{2-[(2,3-Dichloro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid

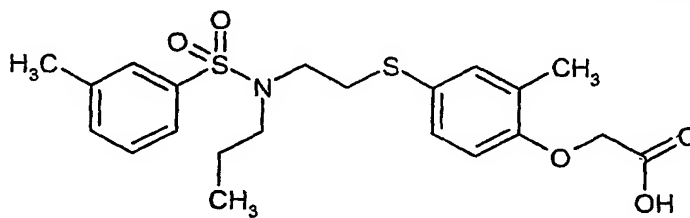


10

Mass spectrum (ES): 492 (M+H)⁺, 490 (M-H)⁻.

Example 121

(2-Methyl-4-{2-[propyl-(toluene-3-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



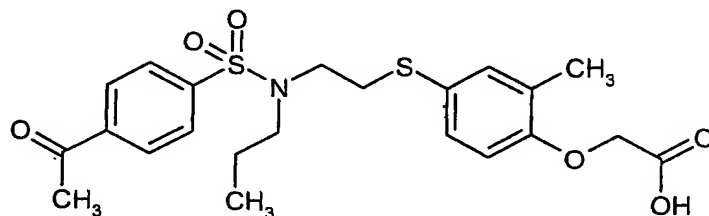
15

Mass spectrum (ES): 438 (M+H)⁺, 436 (M-H)⁻.

-211-

Example 122

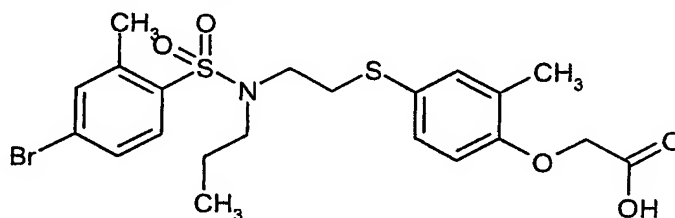
(4-{2-[(4-Acetyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass spectrum (ES): 466 (M+H)⁺, 464 (M-H)⁻.

Example 123

(4-{2-[(4-Bromo-2-methyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



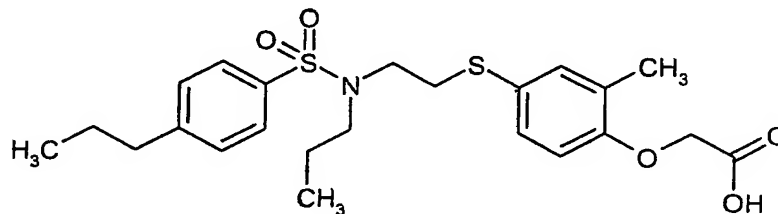
10

Mass spectrum (ES): 516, 518 (M+H)⁺, 514, 516 (M-H)⁻.

Example 124

(2-Methyl-4-{2-[propyl-(4-propyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

15

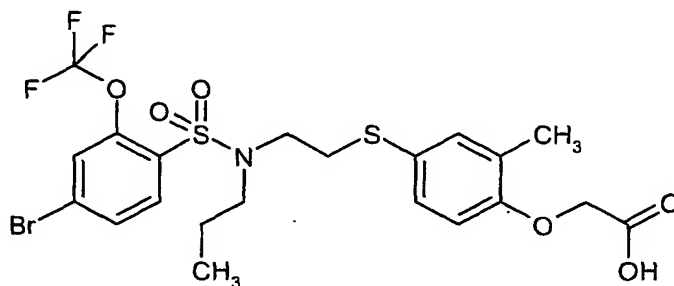


Mass spectrum (ES): 466 (M+H)⁺, 464 (M-H)⁻.

-212-

Example 125

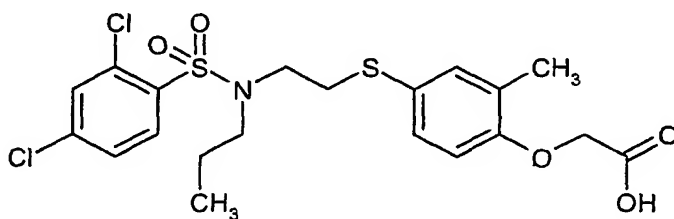
(4-{2-[(4-Bromo-2-trifluoromethoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass spectrum (ES): 586, 588 (M+H)⁺, 584, 585 (M-H)⁻.

Example 126

(4-{2-[(2,4-Dichloro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



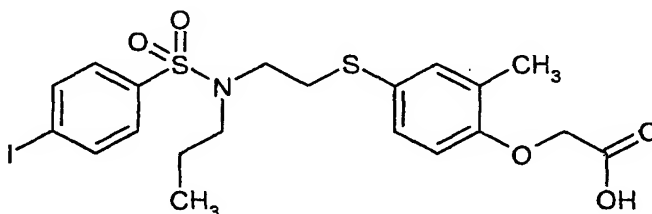
10

Mass spectrum (ES): 492 (M+H)⁺, 490 (M-H)⁻.

Example 127

(4-{2-[(4-Iodo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

15

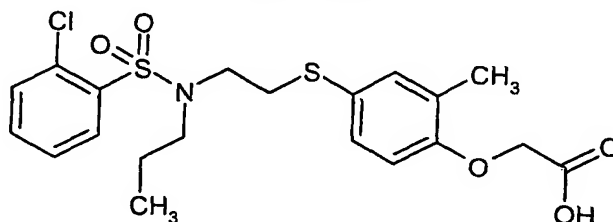


Mass spectrum (ES): 550 (M+H)⁺, 548 (M-H)⁻.

-213-

Example 128

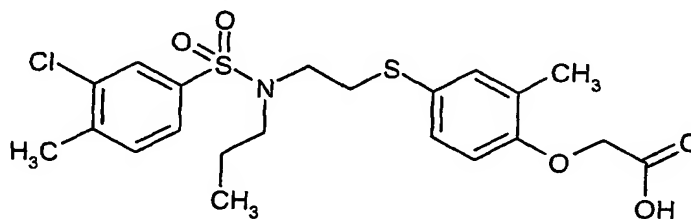
(4-{2-[(2-Chloro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass spectrum (ES): 458 (M+H)⁺, 456 (M-H)⁻.

Example 129

(4-{2-[(3-Chloro-4-methyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

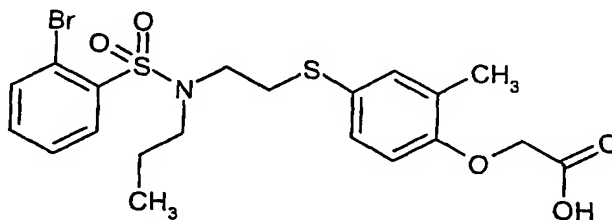


10

Mass spectrum (ES): 472 (M+H)⁺, 470 (M-H)⁻.

Example 130

(4-{2-[(2-Bromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



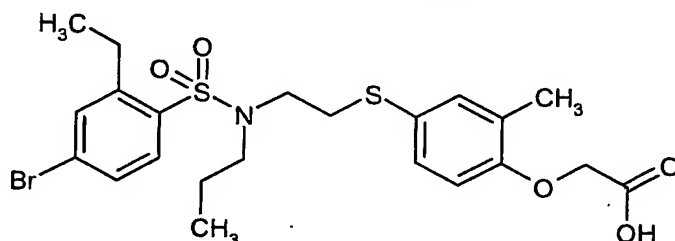
15

Mass spectrum (ES): 502, 504 (M+H)⁺, 500, 502 (M-H)⁻.

-214-

Example 131

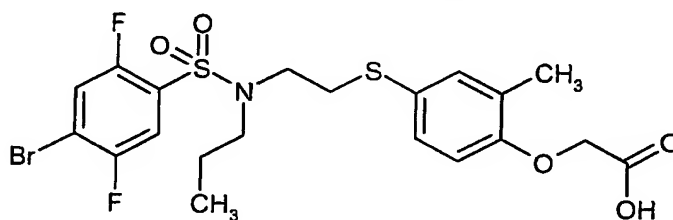
(4-{2-[(4-Bromo-2-ethyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass spectrum (ES): 530, 532 (M+H)⁺, 528, 530 (M-H)⁻.

Example 132

(4-{2-[(4-Bromo-2,5-difluoro-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



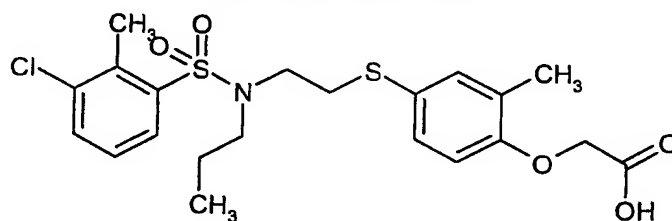
10

Mass spectrum (ES): 538, 540 (M+H)⁺, 536, 538 (M-H)⁻.

Example 133

(4-{2-[(3-Chloro-2-methyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

15

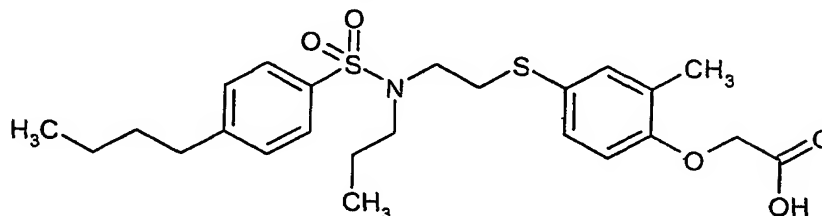


Mass spectrum (ES): 472 (M+H)⁺, 470 (M-H)⁻.

-215-

Example 134

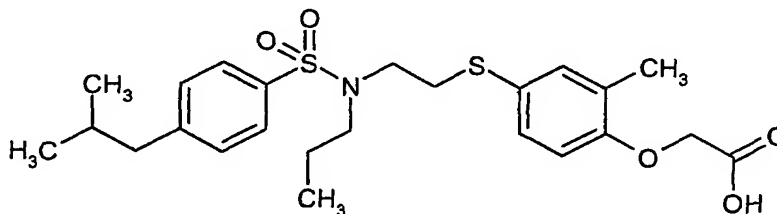
(4-{2-[(4-Butyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass spectrum (ES): 480 (M+H)⁺, 478 (M-H)⁻.

Example 135

(4-{2-[(4-Isobutyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



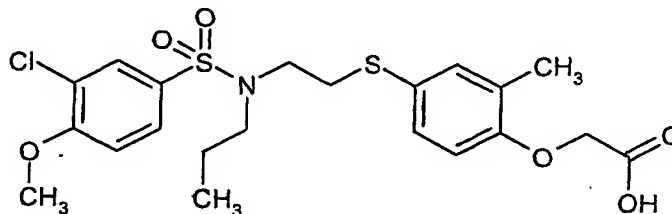
10

Mass spectrum (ES): 480 (M+H)⁺, 478 (M-H)⁻.

Example 136

(4-{2-[(3-Chloro-4-methoxy-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

15

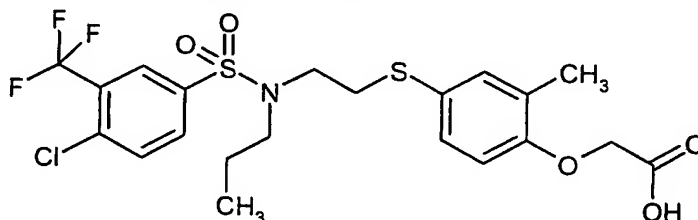


Mass spectrum (ES): 488 (M+H)⁺, 486 (M-H)⁻.

-216-

Example 137

(4-{2-[(4-Chloro-3-trifluoromethyl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



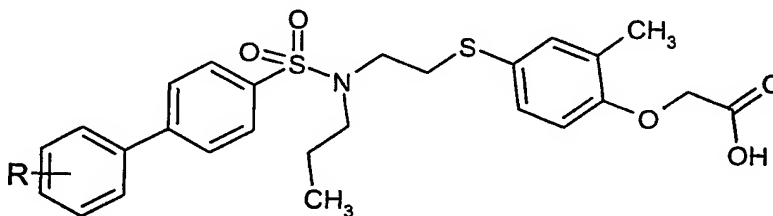
5 Mass spectrum (ES): 526 (M+H)⁺, 524 (M-H)⁻.

Example 138

4-Chloro-3-trifluoromethyl-benzenesulfonyl chloride

10 Add a solution of NaNO_{2(aq)} (10.0 mmole, 1.50 ml) into a suspension of 4-chloro-3-trifluoromethyl aniline (10.0 mmole) in concentrated HCl/glacial acetic acid (3.50 : 1.00, 4.50 ml) at 0°C. Stir for an hour. Transfer the diazonium salt formed above into a saturated solution of SO₂ in glacial HOAc (15.0 ml) at 0°C, then warm up to room temperature for an hour. Pour the reaction mixture into ice water (100 ml), extract with 3 x 50.0 ml ethyl ether. Wash the combined organics with 3 x 100 ml NaHCO_{3(aq)}, 3 x 100 ml brine, dried over Na₂SO₄ and concentrated. Purified by chromatography, eluting with ethyl acetate/hexane (1:9).

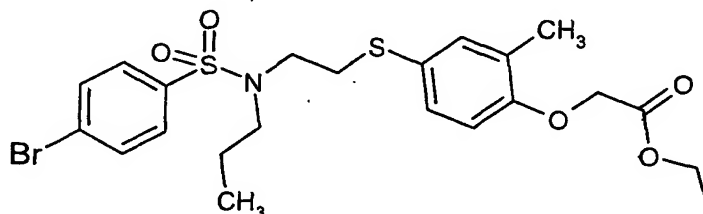
15

Example 139General Procedure (2)

-217-

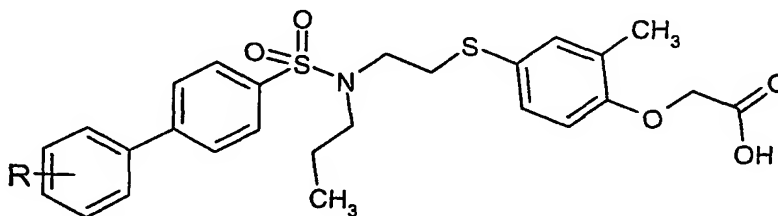
Step A

(4-{2-[(4-Bromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



5 Triethyl amine (0.836 ml, 6.00 mmol) was added to a mixture of 4-bromo-benzenesulfonyl chloride (0.511 g, 2.00 mmole) trifluoroacetic acid salt of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (Example 105, General Procedure (1), Step A) (0.850 g, 2.00 mmol) in methylene chloride (10.0 ml). The reaction was stirred at room temperature overnight. The mixture was diluted with more
10 methylene chloride (10.0 ml) and washed with brine (20.0 ml). The aqueous layer was extracted with 2 x 20.0 ml methylene chloride. The organic extracts were combined, dried over sodium sulfate and concentrated under reduced pressure. Purification by column chromatography, eluting with ethyl acetate: hexane (1:9 to 1:4) and evaporation of solvents afforded the title compound.

15

Step B

The compound of (4-{2-[(4-Bromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (Step A) (0.100 mmol), corresponding substituted benzene boronic acid (0.300 mmol) and cesium fluoride were added to dioxane (2.00 ml). The mixture with was degassed with nitrogen for 15 minutes,
20 and the catalyst PdCl₂(dppf) (0.0200 mmol) was added. The mixture was heated up to 100°C for 16 hours. The catalyst was then removed through a celite pad and the solvent was evaporated *in vacuo*. Purification by column chromatography, eluting with ethyl acetate: hexane (1:9 to 1:4) and evaporation of solvents afforded the substituted biphenyl

-218-

sulfonamide as an ethyl ester. The ethyl ester obtained above was dissolved in MeOH (2.00 ml) and 5.0N NaOH (1.00 ml) was added, and let it stand at room temperature overnight. The organic solvents were evaporated *in vacuo* and the mixture was adjusted to pH 2 to 3 with concentrated HCl. The water was removed using ChemElut CE1005.

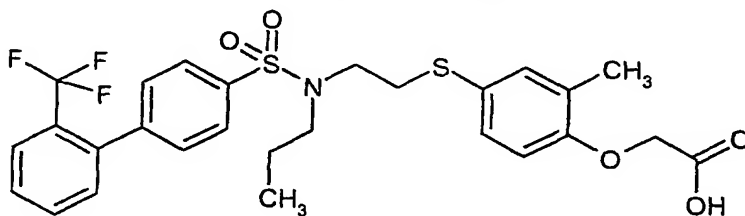
- 5 The ChemElut tube was washed with ethyl acetate (40 ml) and the solution was concentrated to dryness. Purification by preparative HPLC (UV-2), eluting with 0.1% TFA in acetonitrile and lyophilization yielded the title compound.

The following Examples 140-151 were prepared according to the General Procedure (2) as described above by using the appropriate starting material.

10

Example 140

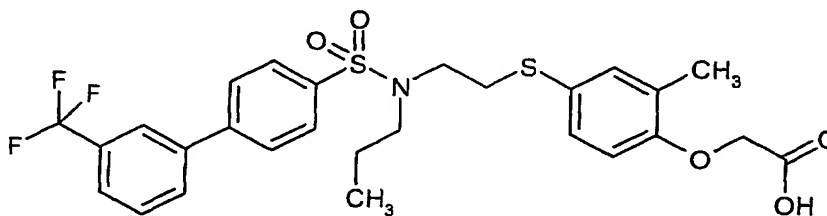
(2-Methyl-4-{2-[propyl-(2'-trifluoromethyl-biphenyl-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



- 15 Mass spectrum (ES): 568 (M+H)⁺, 566 (M-H)⁻.

Example 141

(2-Methyl-4-{2-[propyl-(3'-trifluoromethyl-biphenyl-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



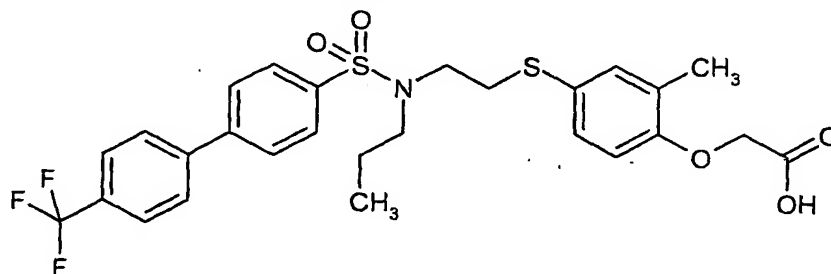
20

- Mass spectrum (ES): 568 (M+H)⁺, 566 (M-H)⁻.

-219-

Example 142

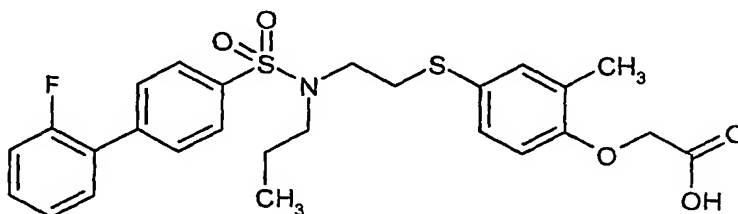
(2-Methyl-4-{2-[propyl-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



5 Mass spectrum (ES): 568 (M+H)⁺, 566 (M-H)⁻.

Example 143

(4-{2-[(2'-Fluoro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid



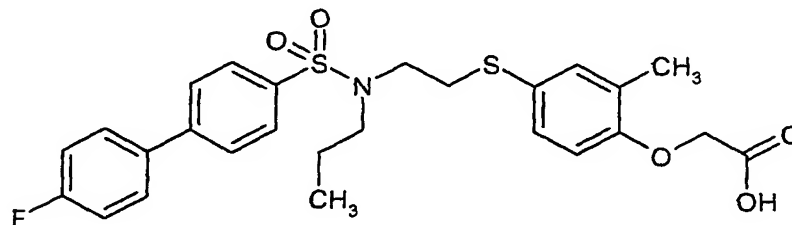
10

Mass spectrum (ES): 518 (M+H)⁺, 516 (M-H)⁻.

Example 144

(4-{2-[(4'-Fluoro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid

15

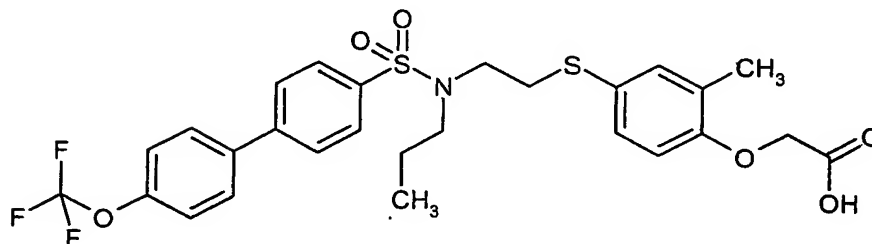


Mass spectrum (ES): 518 (M+H)⁺, 516 (M-H)⁻.

-220-

Example 145

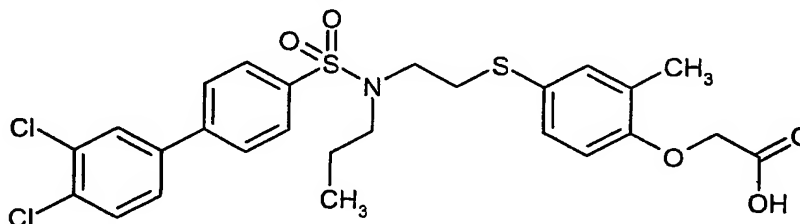
(2-Methyl-4-{2-[propyl-(4'-trifluoromethoxy-biphenyl-4-sulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



5 Mass spectrum (ES): 584 (M+H)⁺, 582 (M-H)⁻.

Example 146

(4-{2-[(3',4'-Dichloro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid

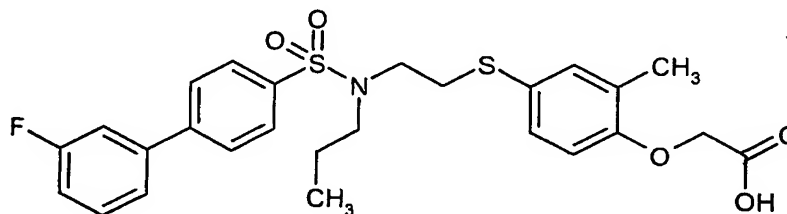


10

Mass spectrum (ES): 568, 570 (M+H)⁺, 566, 568 (M-H)⁻.

Example 147

(4-{2-[(3'-Fluoro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid

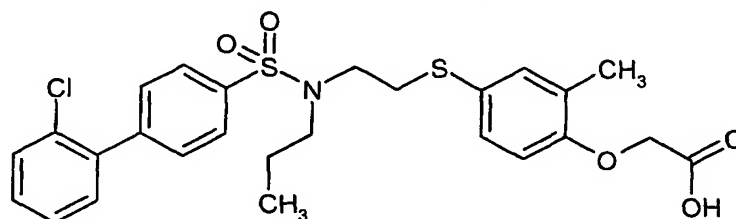


5 Mass spectrum (ES): 518 (M+H)⁺, 516 (M-H)⁻.

-221-

Example 148

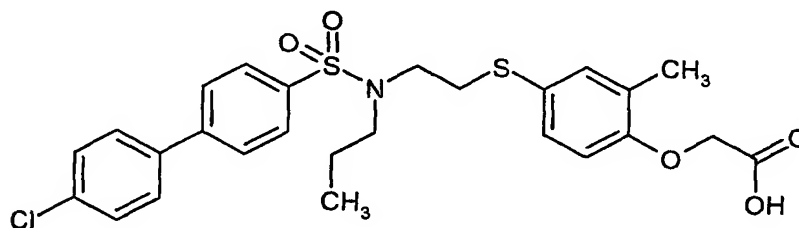
(4-{2-[(2'-Chloro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass spectrum (ES): 534 (M+H)⁺, 532 (M-H)⁻.

Example 149

(4-{2-[(4'-Chloro-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



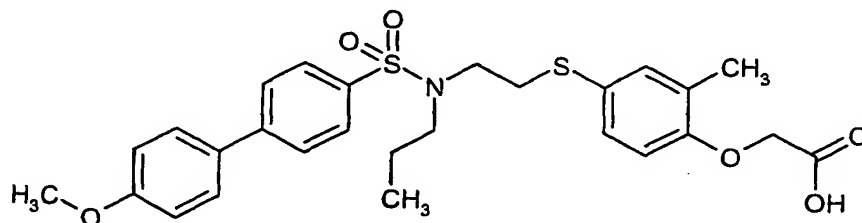
10

Mass spectrum (ES): 534 (M+H)⁺, 532 (M-H)⁻.

Example 150

(4-{2-[(4'-Methoxy-biphenyl-4-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid (2123707, NH1-A03057-182-4)

15

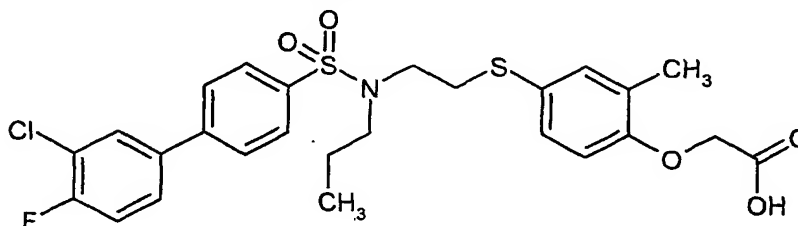


Mass spectrum (ES): 530 (M+H)⁺, 528 (M-H)⁻.

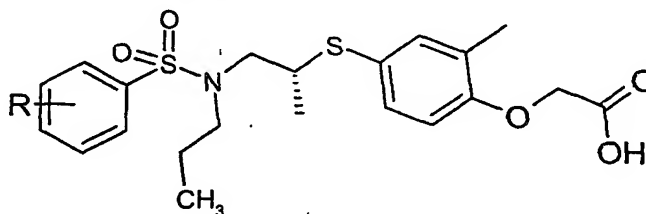
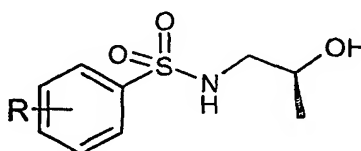
-222-

Example 151

(4-{2-[(3'-Chloro-4'-fluorobiphenyl)-4-sulfonyl]-propyl-amino}-ethylsulfanyl}-2-methylphenoxy)-acetic acid

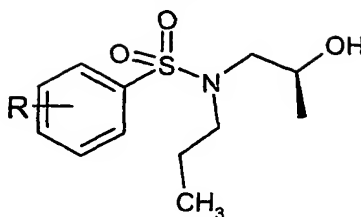


5 Mass spectrum (ES): 552 (M+H)⁺, 550 (M-H)⁻.

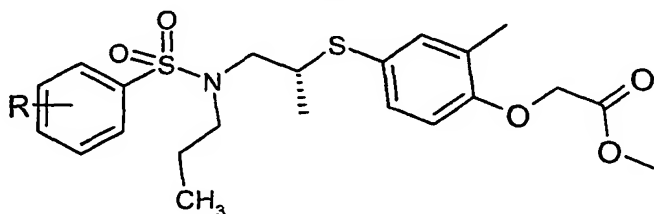
Example 152General Procedure (3a)Step A

A solution of substituted benzenesulfonyl chloride (5.00 mmol) in methylene chloride (20.0 ml) was added into a mixture of (S)-(+)-amino-2-propanol (5.00 mmol) and triethyl amine (15.0 mmol) in methylene chloride (80.0 ml). The mixture was stirred at room temperature for 16 hours. The mixture was washed with 1.0N HCl (100 ml) and brine (2 x 100ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give the title compound, which was used for the next step without further purification.

-223-

Step B

The primary sulfonamide (see Step A) (5.00 mmole) was dissolved in DMF (25.0 ml) and then cesium carbonate (1.95 g, 6.00 mmol) and 1-iodopropane (0.585 ml, 6.00 mmol) were added. The mixture was stirred for 16 hours and then diluted with ethyl acetate (100 ml). The solid was removed through filtration, and the mother liquid was washed with saturated aqueous NH_4Cl (100 ml). The aqueous was extracted back with more ethyl acetate (100 ml). The combined organics were washed with 3 x 200 ml brine, dried over sodium sulfate and concentrated under reduced pressure to provide the title compound.

Step C

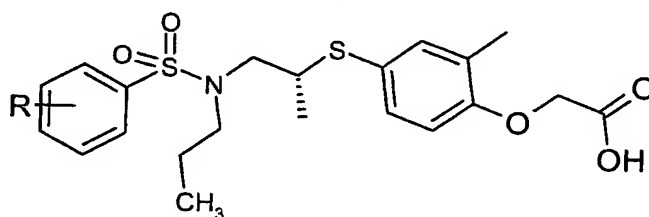
Methanesulfonyl chloride (1.20 mmol) was added dropwise to a mixture of the alcohol obtained from Step B (1.00 mmol) and triethyl amine (1.50 mmol) in DCM (10.0 ml) at 0°C , and the mixture was stirred at 0°C for 2 hours. The mixture was quenched with 1N HCl (100 ml). The aqueous was extracted with DCM (50.0 ml), and the combined organics were washed with 3 x 100 ml brine, dried over sodium sulfate and concentrated under reduced pressure to give a mesylate. The mesylate (1.00 mmol) was dissolved in DMF (3.00 ml). The solution of mesylate was added into a mixture of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (thiophenol headpiece) (1.20 mmol) and potassium carbonate (1.50 mmol) in DMF (3.00 ml) at room temperature, and the mixture was stirred for 16 hours. The mixture was diluted with ethyl acetate (50.0 ml), and the solids were removed by filtration. The mother liquid was washed with saturated aqueous NH_4Cl (50.0 ml), and the aqueous was extracted back with more ethyl acetate (20.0 ml). The combined organics were washed with 3 x 70.0 ml brine, dried over

-224-

sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate: hexane (0-1: 4) and concentration of fractions afforded the title compound.

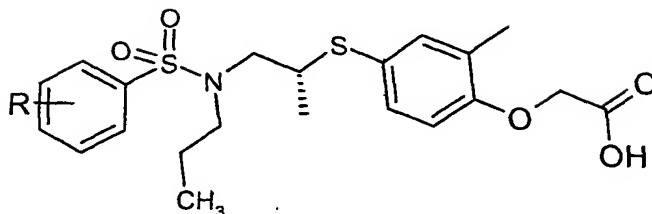
Alternatively, the title compound was prepared by the following procedure. The alcohol obtained from Step B (1.00 mmol) and (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (thiophenol headpiece) (1.00 mmol) were mixed in anhydrous toluene (5.00 ml), and the mixture was cooled to 0°C. Tri-n-butylphosphine (1.20 mmol) and a solution of 1,1'-(azodicarbonyl)-dipiperidine (1.20 mmol) in toluene (5.00 ml) were added to the mixture, which was warmed up to room temperature and stirred for 16 hours. The precipitate was removed through filtration, and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate: hexane (0-1: 4) and concentration of fractions afforded the title compound.

Step D

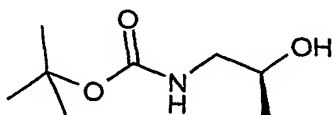


The ethyl ester (Step C, 0.200 mmol) was dissolved in MeOH (2.00 ml) and 5.0N NaOH (1.00 ml) was added, and the mixture was let stand at room temperature overnight. The organic solvents were evaporated *in vacuo*, and adjusted to pH 2 to 3 with concentrated HCl. The water was removed using ChemElut CE1005, and the Chem elut tube was washed with ethyl acetate (40.0 ml). The solution was concentrated to dryness afford the title compound.

-225-

Example 153General Procedure (3b)Step A

5 (2-Hydroxy-propyl)-carbamic acid tert-butyl ester

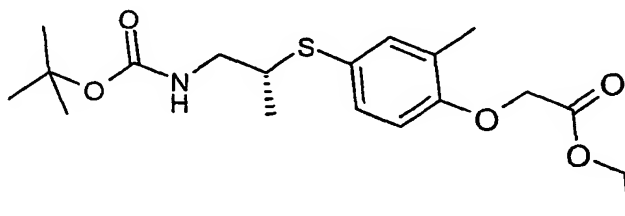


Triethyl amine (22.0 mmol) was added to a mixture of di-tert-butyl dicarbonate (20.0 mmole) and (S)-(+)-1-amino-propanol (20.0 mmol) in MeOH (100 ml). The mixture was stirred at room temperature for 16 hours. The methanol was

10 evaporated, the residue was re-dissolved in ethyl acetate (100 ml) and washed with brine (3 x 100ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give the title compound, which was used for the next step without further purification.

Step B

15 [4-(2-tert-Butoxycarbonylamino-1-methyl-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester



(2-Hydroxy-propyl)-carbamic acid tert-butyl ester (Step B, (10.0 mmol) and (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (thiophenol headpiece) (10.5 mmol) were mixed in anhydrous toluene (25.0 ml), and the mixture was cooled to 0°C.

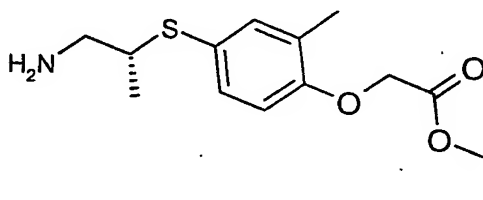
20 Tri-n-butylphosphine (12.0 mmol) and a solution of 1.1'-(azodicarbonyl)-dipiperidine (12.0 mmol) in toluene (25.0 ml) were added to the mixture, which was warmed up to room temperature and stirred for 16 hours. The precipitate was removed through filtration, and concentrated under reduced pressure. Purification by flash

-226-

chromatography, eluting with ethyl acetate: hexane (0-1: 4) and concentration of fractions afforded the title compound.

Step C

[4-(2-Amino-1-methyl-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester

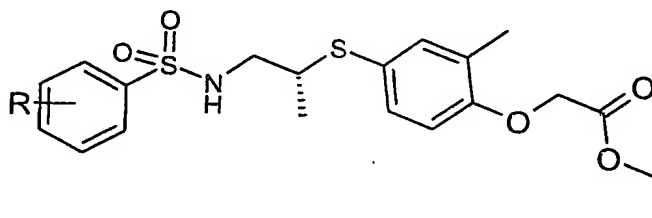


5

Trifluoroacetic acid (17 ml) was added dropwise to a mixture of [4-(2-tert-butoxycarbonylamino-1-methyl-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (Step B, 10.0 mmol) and dimethylethyl silane (30.0 mmol) in methylene chloride (100 ml) at room temperature. The mixture was stirred for 2 hours, which was then washed with saturated NaHCO₃ (3 x 100 ml), dried over Na₂SO₄ and concentrated on a rotavapor to give the title compound. The compound was used for the next step directly without purification.

10

Step D

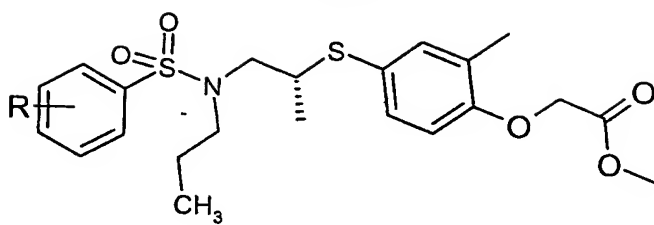


15

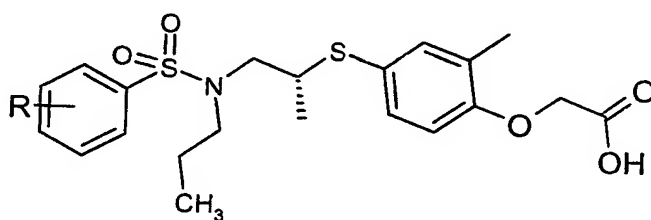
A solution of substituted benzene sulfonyl chloride (5.00 mmole) was added to a mixture of [4-(2-amino-1-methyl-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (Step C, 5.00 mmol) and Et₃N (15.0 mmol) in methylene chloride (40.0 ml) at 0°C, and the mixture was warmed up and stirred the reaction at room temperature for 16 hours. The mixture was washed with 1N HCl (50.0 ml) and brine (3 x 50.0 ml), dried over sodium sulfate and concentrated under reduced pressure. Purification by column chromatography, eluting with ethyl acetate: hexane (2:3) and evaporation of solvents afforded the title compound.

20

-227-

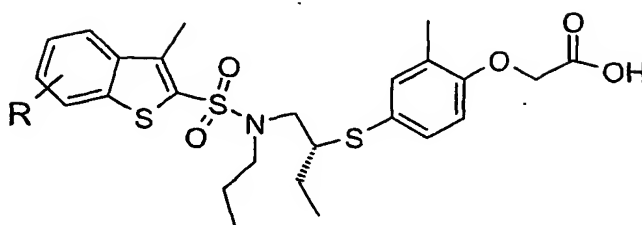
Step E

The primary sulfonamide (see Step D) (5.00 mmol) was dissolved in DMF (25.0 ml), and cesium carbonate (1.95 g, 6.00 mmol) and 1-iodopropane (0.585 ml, 6.00 mmol) were added. The mixture was stirred for 16 hours, and then diluted with ethyl acetate (100 ml). The solid was removed through filtration, and the mother liquid was washed with saturated aqueous NH_4Cl (100 ml). The aqueous was extracted back with more ethyl acetate (100 ml). The combined organics were washed with 3 x 200 ml brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate: hexane (0-1: 4) and concentration of fractions afforded the title compound.

Step F

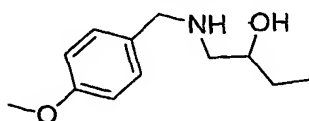
The ethyl ester (1.00 mmol) obtained from Step E was dissolved in MeOH (10.0 ml) and 5.0N NaOH (5.00 ml) was added and the mixture was let stand at room temperature overnight. The organic solvents were evaporated *in vacuo*, and adjusted to pH 2 to 3 with concentrated HCl. The water was removed using ChemElut CE1010, which was washed with ethyl acetate (200 ml). The solution was then concentrated to dryness give the title compound.

-228-

Example 154General Procedure (3c)Step A

5

1-(4-Methoxy-benzylamino)-butan-2-ol



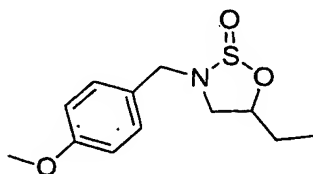
1-amino-2-butanol (0.157mol) was added to a 0 °C suspension of *p*-anisaldehyde (, 0.172mol) and sodium sulphate (0.188mol) in dry CH₂Cl₂ (150 mL). The resulting mixture was stirred at room temperature for one hour, filtered, and concentrated *in vacuo*. The residue was diluted with 4Å molecular sieve-dried ethanol (100 mL) and cooled to 0 °C. Sodium borohydride (0.157mol) was added to the solution in two portions and the resulting mixture was stirred at room temperature for two hours. The resultant mixture was concentrated *in vacuo*, and then partitioned between CH₂Cl₂ and 1 N NaOH. The organic layer was acidified to pH 10 with 1N HCl, dried over sodium sulphate, and concentrated *in vacuo* to give >99% yield of 1-(4-methoxy-benzylamino)-butan-2-ol. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 3.78 s, 3H), 3.72, 3.68 (ABq, 2H, *J* = 12.4 Hz) 3.56-3.50 (m, 1H), 2.71 (dd, 1H, *J* = 12.3 Hz, 2.8 Hz), 2.49 (dd, 1H, *J* = 12.3 Hz, 9.6 Hz), 1.46-1.38 (m, 2H), 0.92t, 3H, *J* = 7.4 Hz). MS [EI+] 210 (M+H)⁺.

20

-229-

Step B

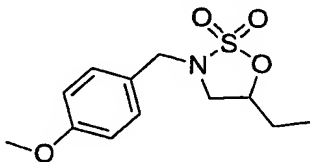
5-Ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2-oxide



Thionyl chloride (20.29mol) was added dropwise to a -78 °C solution of 1-(4-methoxy-benzylamino)-butan-2-ol (0.16mol) and triethylamine (0.59mol) in dry CH₂Cl₂. The resulting mixture was stirred at -78 °C for 40 minutes, and then warmed to 0 °C for five hours. The mixture was diluted with water and extracted with CH₂Cl₂. The organic layers were combined, dried over sodium sulphate, and concentrated *in vacuo*. The residue was purified by flash chromatography using 11% acetone in hexanes as eluent, and gave 15.35 g (39%) of 5-ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2-oxide. ¹H NMR (400 MHz, CDCl₃) δ 7.28 (dd, 2H, *J* = 8.5 Hz, 4.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 5.02-4.96 (m, 1H), 4.54-4.47 (m, 1H), 4.24, 4.22 (ABq, 2H, *J* = 5.9 Hz isomer 1), 3.91, 3.79 (ABq, 2H, *J* = 13.3 Hz isomer 2), 3.79 s, 3H), 3.41, 3.39 (ABq, 1H, *J* = 6.1 Hz isomer 1) 3.29, 3.27 (ABq, 1H, *J* = 6.1 Hz isomer 2) 3.12, 3.10 (ABq, 1H, *J* = 9.6 Hz isomer 1) 2.92, 2.90 (ABq, 1H, *J* = 9.6 Hz isomer 2) 1.98-1.77 (m, 2H isomer 1), 1.76-1.57 (m, 2H isomer 2), 1.00(t, 3H, *J* = 7.5 Hz), 0.94(t, 3H, *J* = 7.5 Hz). *R*_f = 0.31 in 33% acetone in hexanes.

Step C

5-Ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2,2-dioxide



20

Ruthenium (III) chloride (1.32 mmol) was added to a biphasic solution of 5-ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2-oxide (15.35 g, 60.1 mmol), sodium periodate (0.12mol), CCl₄ (150 mL), CH₃CN (150 mL), and water (180 mL). The resulting mixture was stirred at room temperature for three hours, and then filtered through a pad of celite. The filtrate was diluted with CH₂Cl₂ and washed with sodium thiosulphate solution and water. The residue was purified by flash chromatography, using

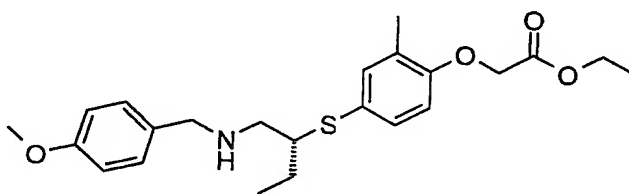
25

-230-

11% acetone in hexanes as eluent, and gave 14.33 g (88 %) of 5-ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2,2-dioxide. This material was resolved using chiral HPLC (Chiralpak OJ 4.6 x 150 mm, 30/70 alcohol/heptane, 0.6 mL/min, 240 nm UV setting) to give enantiomers: isomer 1, (>98% ee, *R*) and isomer 2, (>98% ee *S*). ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 4.69-4.62 (m, 1H), 4.23, 4.03 (ABq, 2H, *J* = 13.4 Hz), 3.80 (s, 3H), 3.35 (dd, 1H, *J* = 9.5 Hz, 6.2 Hz) 3.03 (dd, 1H, *J* = 9.5 Hz, 8.2 Hz) 1.92-1.81 (m, 1H), 1.75-1.65 (m, 1H), 0.98t, 3H, *J* = 7.5 Hz). *R*_f = 0.31 in 33% acetone in hexanes.

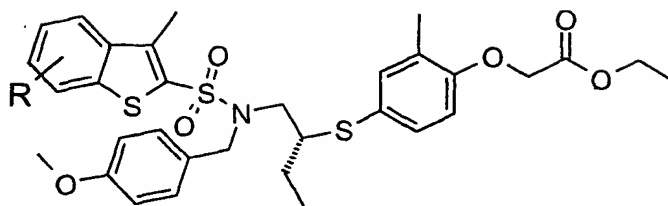
Step D

(4-{1-[(4-Methoxy-benzylamino)-methyl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester

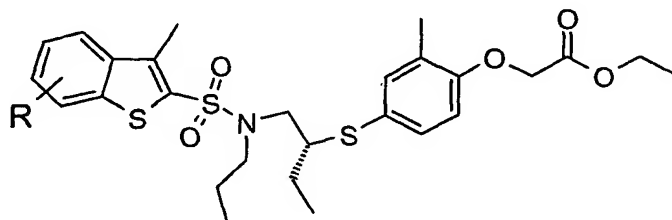


A 0 °C solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (29.43 mmol) in dimethylformamide (10 mL) was treated with sodium hydride (29.43 mmol). The suspension was flushed with N₂ while stirring for 15 minutes at 0 °C. 5-Ethyl-3-(4-methoxy-benzyl)-[1,2,3]oxathiazolidine 2,2-dioxide (19.62 mmol) in dimethylformamide (10 mL) was added and the resulting mixture was heated at 50 °C for 4h. The mixture was cooled to ambient temperature, diluted with diethyl ether, and stirred with 1N HCl. After 8h, the mixture was basified to pH7 with saturated aqueous sodium bicarbonate solution. The organic layer was washed with water and brine, dried over sodium sulphate, treated with trifluoroacetic acid (58.86 mmol), and concentrated *in vacuo* to provide 15.6 g (84%) of the title compound as a TFA salt. ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, 2H, *J* = 9.1 Hz), 6.95 (d, 1H, *J* = 1.4 Hz), 6.87-6.84 (m, 1H), 6.85 (d, 2H, *J* = 8.7 Hz), 6.43 (d, 1H, *J* = 9.1 Hz), 4.55 (s, 2H), 4.20 (p, 2H, *J* = 7.0 Hz), 4.20-4.06 (m, 2H), 3.74 (s, 3H), 3.09-3.02 (m, 2H), 2.86-2.74 (m, 1H), 2.09 (s, 3H), 1.42 (p, 2H, *J* = 7.0 Hz), 1.22 (t, 3H, *J* = 7.0 Hz), 0.95 (t, 3H, *J* = 7.0 Hz). MS [EI⁺] 418 (M+H)⁺.

-231-

Step E

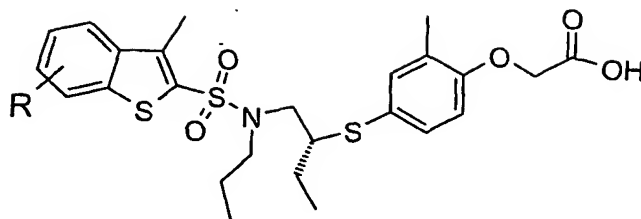
A 0°C solution of (4-{1-[4-methoxy-benzylamino)-methyl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (18.97 mmol) in
 5 dichloromethane (200 mL) was treated with triethylamine (151.76 mmol). An appropriately substituted sulfonyl chloride (24.6 mmol) was added all at once and the reaction mixture was warmed to ambient temperature for 1.5h. The reaction mixture was diluted with dichloromethane and washed with 1N HCl. The organic layers were combined, dried over MgSO₄, and concentrated *in vacuo*. The crude material was
 10 purified by flash chromatography to provide the title compound.

Step F

Trifluoroacetic acid (70 mL, 1 mmol) was added dropwise to a solution of the benzylamine (7.19 mmol) and triethylsilane (144 mmol). The resulting solution was
 15 stirred at ambient temperature for 1h, then concentrated *in vacuo*. The reaction residue was diluted with diethyl ether and washed with saturated aqueous sodium bicarbonate and water. The organic layer was dried over sodium sulphate and concentrated *in vacuo*.

1-Iodopropane (21.8 mmol) was added to a suspension of the crude amine (21.8 mmol) in dimethylformamide (100 mL). The resulting mixture was heated to 50 °C
 20 for 2h, and then cooled to ambient temperature and diluted with diethyl ether. The organic layer was washed with 1N HCl, water, and brine, dried over MgSO₄, and concentrated *in vacuo* to provide the title compound.

-232-

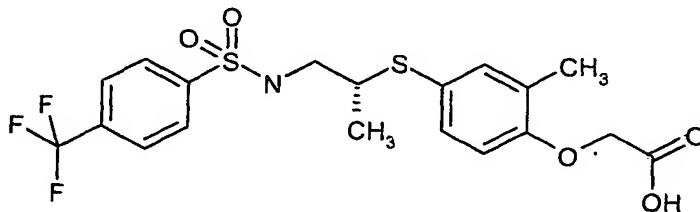
Step G

A solution of the ethyl ester (3.79 mmol) and 5N NaOH (2 mL) in ethanol (20 mL) was refluxed under nitrogen for 0.5h, cooled to ambient temperature, and concentrated in vacuo. The residue was diluted with 1N HCl, extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated *in vacuo* to provide the title compound.

The following Examples 155 to 160 were prepared according to the General Procedures (3a), (3b) and (3c) as described above in Examples 152 to 154 by using an appropriate starting material.

Example 155

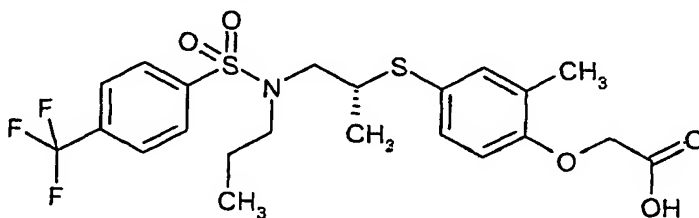
{2-Methyl-4-[1-methyl-2-(4-trifluoromethyl-benzenesulfonylamino)-ethylsulfanyl]-phenoxy}-acetic acid



Mass spectrum (ES): 464 (M+H)⁺, 462 (M-H)⁻.

Example 156

(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

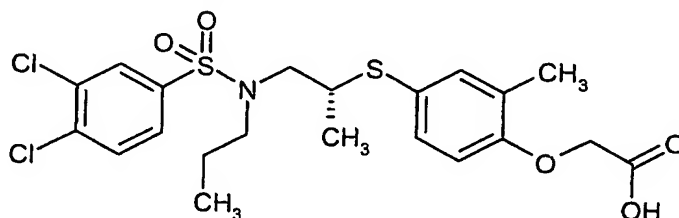


Mass spectrum (ES): 506 (M+H)⁺, 504 (M-H)⁻.

-233-

Example 157

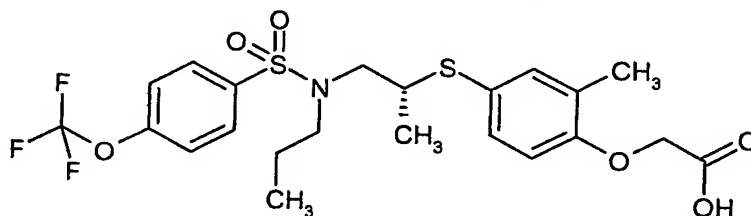
(4-{2-[(3,4-Dichloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass spectrum (ES): 506 (M+H)⁺, 504 (M-H)⁻.

Example 158

(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



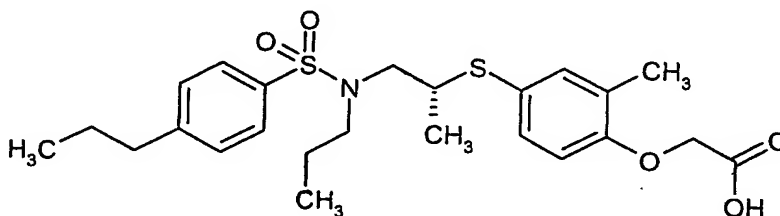
10

Mass spectrum (ES): 522 (M+H)⁺, 520 (M-H)⁻.

Example 159

(2-Methyl-4-{1-methyl-2-[propyl-(4-propyl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

15

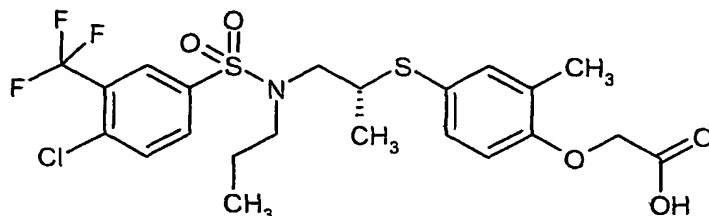


Mass spectrum (ES): 480 (M+H)⁺, 478 (M-H)⁻.

-234-

Example 160

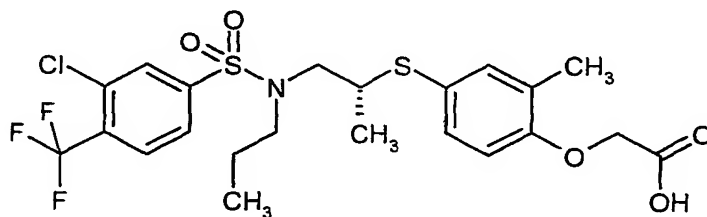
(4-{2-[(4-Chloro-3-trifluoromethyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 Mass spectrum (ES): 540 (M+H)⁺, 538 (M-H)⁻.

Example 161

(4-{2-[(3-Chloro-4-trifluoromethyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



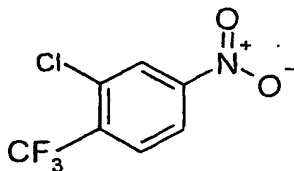
10

Mass spectrum (ES): 540 (M+H)⁺, 538 (M-H)⁻.

15 The title compound was prepared by using the intermediate 3-chloro-4-trifluoromethyl-benzenesulfonyl chloride, which was prepared as described below and following General Procedure 3(a) or 3(b) as described in Examples 152 and 153.

Step A

2-Chloro-4-nitro-1-trifluoromethyl-benzene



20

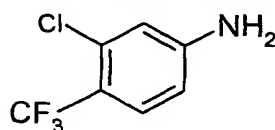
1-Bromo-2-chloro-4-nitrobenzene (1.86 g, 7.86 mmol) and CuI (0.225 g, 1.18 mmole) were mixed in anhydrous DMF (50 ml), and degassed with nitrogen for 15 minutes. Methyl fluorosulphonyl difluoroacetate (3.53 g, 23.6 mmol) was added, and the

-235-

mixture was heated at 80°C for 16 hours. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate (100 ml) and brine (100 ml). The aqueous layer was extracted with more ethyl acetate (100 ml). The combined organics were washed with 3 x 200 ml brine, dried over Na₂SO₄, concentrated, and purified by chromatography, eluting with ethyl acetate/hexane (1:9).

Step B

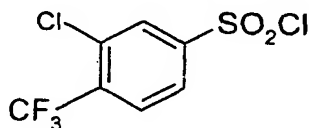
3-Chloro-4-trifluoromethyl-phenylamine



Tin(II) chloride dihydrate (4.97 mmol) in one portion was added to a solution of 2-chloro-4-nitro-1-trifluoromethyl-benzene (4.14 mmole) in methanol at room temperature, and the mixture was stirred for 16 hours. The mixture was concentrated *in vacuo*, and purified by chromatography, eluting with ethyl acetate/hexane (1:4 to 2:3) to give the title compound.

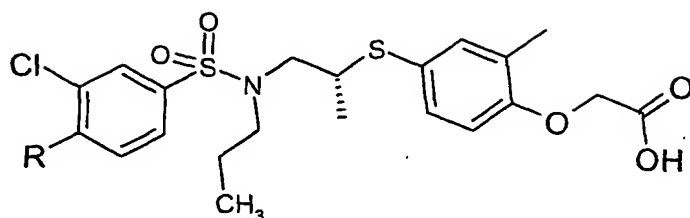
Step C

3-Chloro-4-trifluoromethyl-benzenesulfonyl chloride



A solution of NaNO_{2(aq)} (4.00 mmole, 1.00 ml) was added to a suspension of 3-chloro-4-trifluoromethyl aniline (Step B) (4.00 mmole) in concentrated HCl/glacial acetic acid (3.50 : 1.00, 4.50 ml) at 0°C, and the mixture was stirred for an hour. The diazonium salt formed above was transferred into a saturated solution of SO₂ in glacial HOAc (15.0 ml) at 0°C, and the mixture was warmed up to room temperature for an hour. The mixture was poured into ice water (100 ml) and extracted with 3 x 50.0 ml ethyl ether. The combined organics were washed with 3 x 100 ml NaHCO_{3(aq)}, 3 x 100 ml brine, dried over Na₂SO₄, concentrated, and purified by chromatography, eluting with ethyl acetate/hexane (1:9).

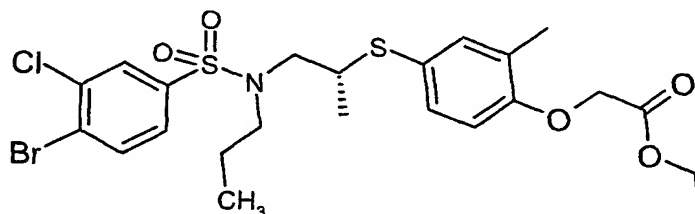
-236-

Example 162General Procedure (4)

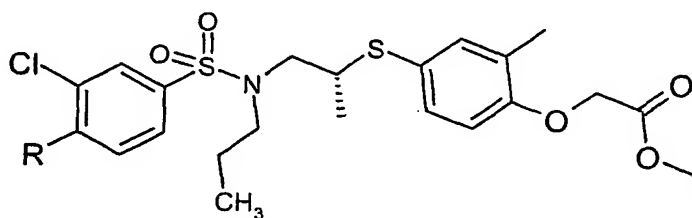
5

Step A

(4-{2-[(4-Bromo-3-chloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



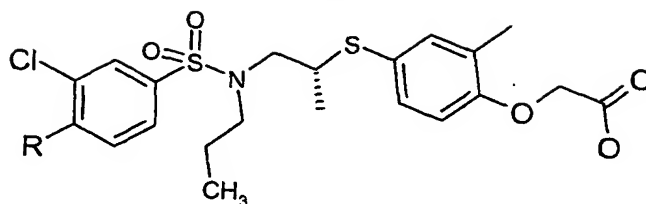
10 The titled compound can be prepared following General Procedure(3b),
Steps A-E as described in Example 153.

Step B

15 Dissolve (4-{2-[(4-bromo-3-chloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (0.200 mmol) in THF (2.00 ml) at room temperature. Degas the solution with nitrogen gas for 15 minutes, then add the catalyst PdCl₂(dppf) (0.0100 mmol) and CuI (0.0120 mmol) subsequently. Inject corresponding alkyl zinc bromide in THF (0.5M, 0.6 ml) and then stir for 3 hours.

20 Remove the solvent on rota vapor. Partition the residue between ethyl acetate (20 ml) and 1N HCl_(aq) (20 ml), wash the organic layer with brine (3 x 20 ml), dried over Na₂SO₄ and concentrated. Purification by column chromatography, eluting with ethyl acetate: hexane (1:4) to provide the title compound.

-237-

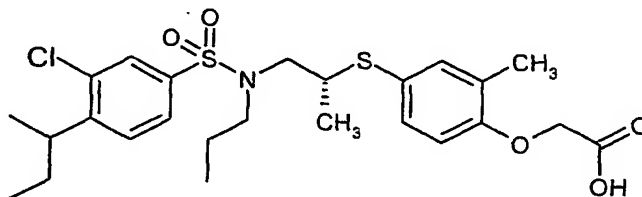
Step C

Dissolve the ethyl ester (1.00 mmol) obtained from Step B in MeOH (10.0 ml) and add 5.0N NaOH (5.00 ml), stand at room temperature overnight. Evaporate the organic solvents *in vacuo*, adjust pH = 2 to 3 with concentrated HCl. Remove the water using ChemElut CE1010. Wash the Chem elut tube with ethyl acetate (100 ml) and concentrate the solution to dryness give the title compound.

The following Examples 163 to 166 were prepared according to the General Procedure (4) as described above by using the indicated starting material.

Example 163

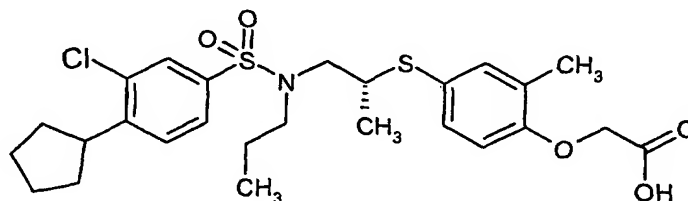
(4-{2-[(4-sec-Butyl-3-chloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



Mass spectrum (ES): 528 (M+H)⁺, 526 (M-H)⁻.

Example 164

(4-{2-[(3-Chloro-4-cyclopentyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

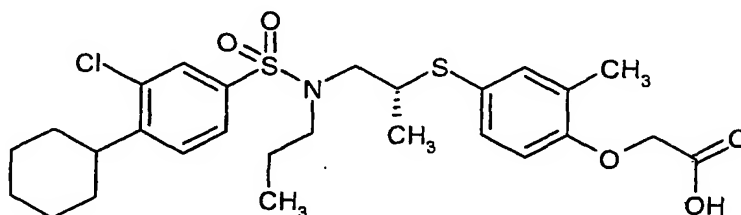


Mass spectrum (ES): 540 (M+H)⁺, 538 (M-H)⁻.

-238-

Example 165

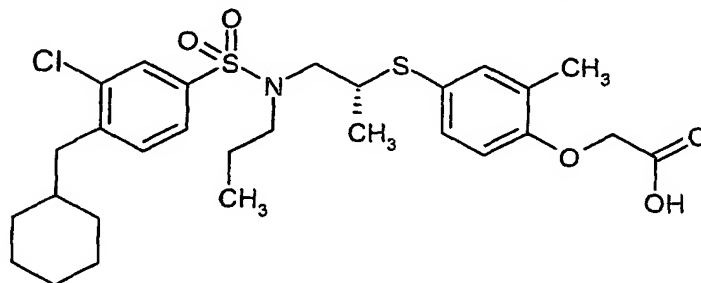
(4-{2-[(3-Chloro-4-cyclohexyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



Mass spectrum (ES): 554 (M+H)⁺, 552 (M-H)⁻.

Example 166

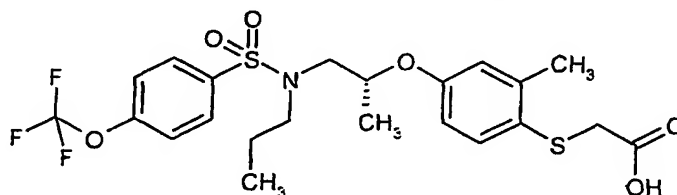
(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid



Mass spectrum (ES): 568 (M+H)⁺, 566 (M-H)⁻.

Example 167

(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-ethoxy}-phenylsulfanyl)-acetic acid



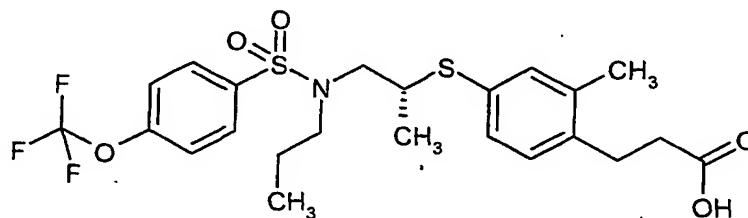
The title compound was prepared according to General Procedure (3a) as described in Example 152 using (4-hydroxy-2-methyl-phenylsulfanyl)-acetic acid ethyl

-239-

ester instead of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (thiophenol headpiece). MS (ES): 522 (M+H)⁺, 520 (M-H)⁻.

Example 168

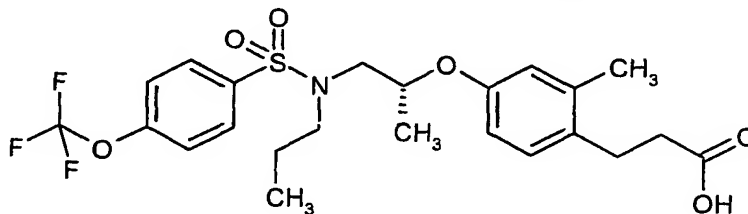
5 3-(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-ethylsulfanyl}-phenyl)-propionic acid



The title compound was prepared according to General Procedure (3a) as described in Example 152 using 3-(4-mercapto-2-methyl-phenyl)-propionic acid methyl ester instead of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (thiophenol headpiece). MS (ES): 520 (M+H)⁺, 518 (M-H)⁻.

Example 169

15 3-(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-ethoxy}-phenyl)-propionic acid

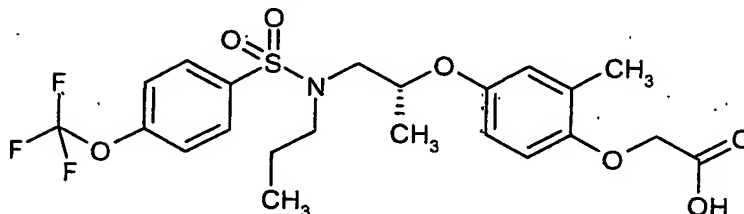


The title compound was prepared according to General Procedure (3a) as described in Example 152 using 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester instead of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (thiophenol headpiece). MS (ES): 504 (M+H)⁺, 502 (M-H)⁻.

-240-

Example 170

(2-Methyl-4-{1-methyl-2-[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-ethoxy}-phenoxy)-acetic acid

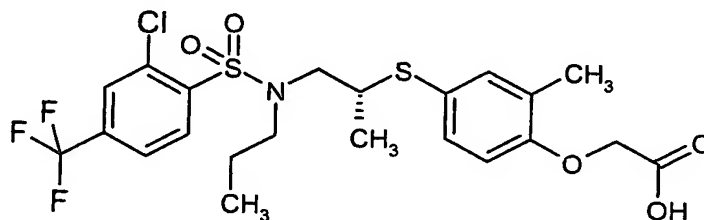


5 The title compound was prepared according to General Procedure (3a) as described in Example 152 using (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester instead of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (thiophenol headpiece). MS (ES): 506 (M+H)⁺, 504 (M-H)⁻.

10

Example 171

(4-{2-[(2-Chloro-4-trifluoromethyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

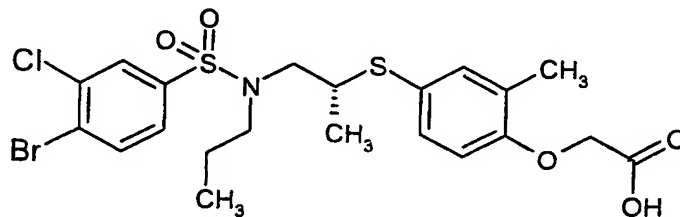


MS (ES): 540 (M+H)⁺, 538 (M-H)⁻.

15

Example 172

(4-{2-[(4-Bromo-3-chloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



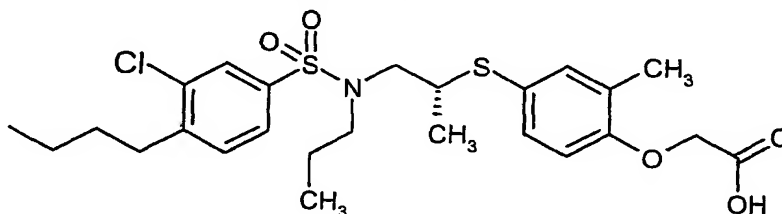
20 MS (ES): 550, 552 (M+H)⁺, 548, 550 (M-H)⁻.

-241-

The following Examples 173 and 174 were prepared according to the General Procedure (3b), Step A to Step E as described in Example 153 and the General Procedure (2) as described in Example 139 using (4-{2-[(4-bromo-3-chloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester instead of (4-{2-[(4-bromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester.

Example 173

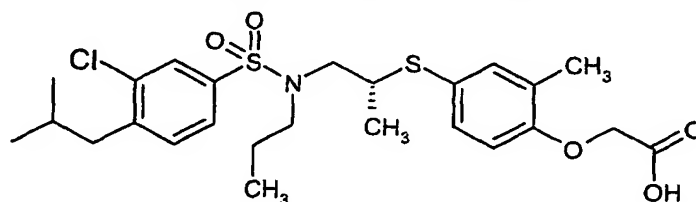
(4-{2-[(4-Butyl-3-chloro-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



MS (ES): 528 (M+H)⁺, 526 (M-H)⁻.

Example 174

(4-{2-[(3-Chloro-4-isobutyl-benzenesulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



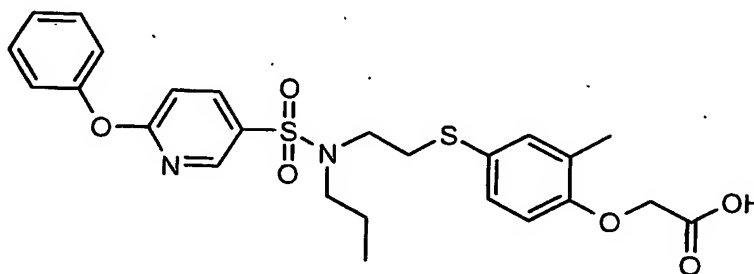
Mass spectrum (ES): 528 (M+H)⁺, 526 (M-H)⁻.

The following Examples 175 to 183 were prepared according to General Procedure (1) as described in Example 105.

-242-

Example 175

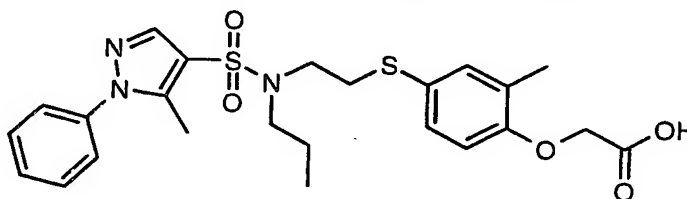
(2-Methyl-4-{2-[(6-phenoxy-pyridine-3-sulfonyl)-propyl-amino]-ethylsulfanyl}
phenoxy)-acetic acid



5 The title compound was prepared from 6-phenoxy-pyridine-3-sulfonyl chloride to afford 155 mg (64%). MS (ES⁺) m/z: 517 (M+1).

Example 176

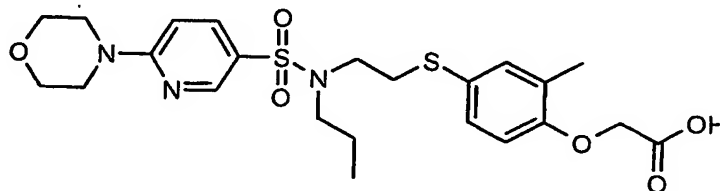
(2-Methyl-4-{2-[(5-methyl-1-phenyl-1H-pyrazole-4-sulfonyl)-propyl-amino]-
ethylsulfanyl}-phenoxy)-acetic acid



10 The title compound was prepared from 5-methyl-1-phenyl-1H-pyrazole-4-sulfonyl chloride to afford 175 mg (74%). MS (ES⁺) m/z: 504 (M+1).

Example 177

(2-Methyl-4-{2-[(6-morpholin-4-yl-pyridine-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-
phenoxy)-acetic acid



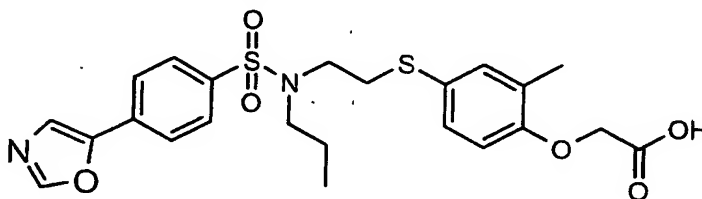
15 The title compound was prepared from 6-morpholin-4-yl-pyridine-3-sulfonyl chloride to afford 153 mg (64%). MS (ES⁺) m/z: 510 (M+1).

20

-243-

Example 178

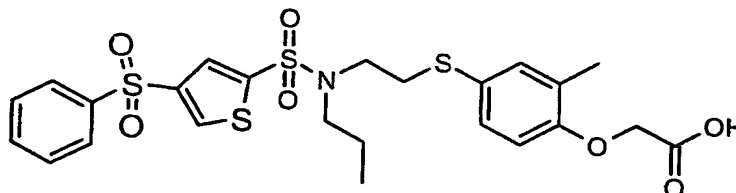
(2-Methyl-4-{2-[(4-oxazol-5-yl-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid



5 The title compound was prepared from 4-oxazol-5-yl-benzenesulfonyl chloride to afford 154 mg (67%). MS (ES⁺) m/z: 491 (M+1).

Example 179

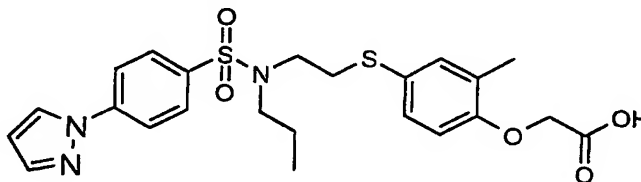
10 (4-{2-[(4-Benzenesulfonyl-thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



The title compound was prepared from 4-Benzenesulfonyl-thiophene-2-sulfonyl chloride to afford 182 mg (68%). MS (ES⁺) m/z: 570 (M+1).

Example 180

15 (2-Methyl-4-{2-[propyl-(4-pyrazol-1-yl-benzenesulfonyl)-amino]-ethylsulfanyl}-phenoxy)-acetic acid

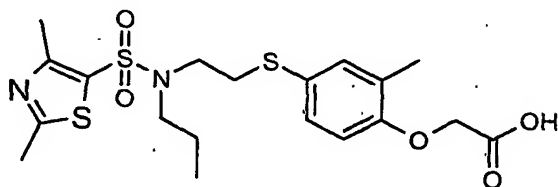


20 The title compound was prepared from 4-pyrazol-1-yl-benzenesulfonyl chloride to afford 148 mg (64%). MS (ES⁺) m/z: 490 (M+1).

-244-

Example 181

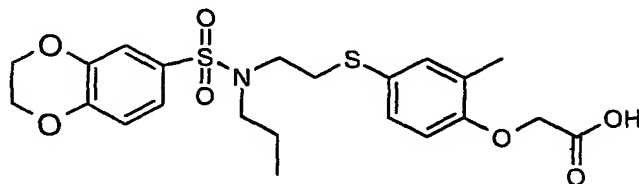
(4-{2-[(2,4-Dimethyl-thiazole-5-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 The title compound was prepared from 2,4-dimethyl-thiazole-5-sulfonyl chloride to afford 80 mg (37%). MS (ES⁺) m/z: 459 (M+1).

Example 182

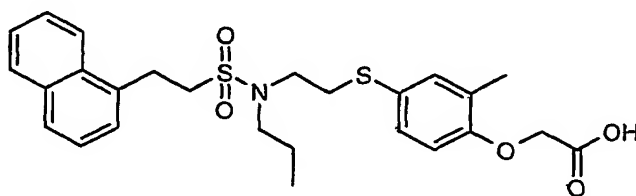
10 (4-{2-[(2,3-Dihydro-benzo[1,4]dioxine-6-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



The title compound was prepared from 2,3-dihydro-benzo[1,4]dioxine-6-sulfonyl chloride to afford 38 mg (17%). MS (ES⁻) m/z: 480 (M-1).

Example 183

15 (2-Methyl-4-{2-[(2-naphthalen-1-yl-ethanesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

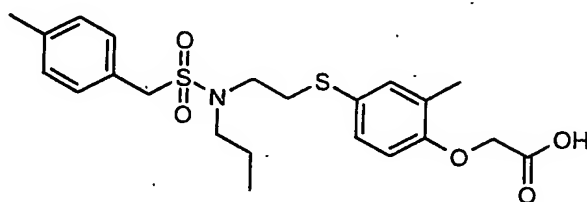


20 The title compound was prepared from 2-Naphthalen-1-yl-ethanesulfonyl chloride to afford 26 mg (12%). MS (ES⁻) m/z: 500 (M-1).

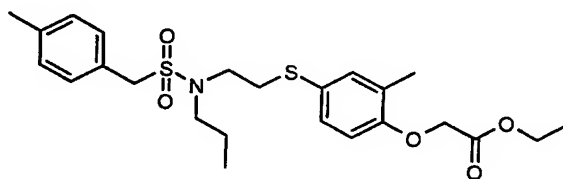
-245-

Example 184

{2-Methyl-4-[2-(propyl-p-tolylmethanesulfonyl-amino)-ethylsulfanyl]-phenoxy}-acetic acid

Step A

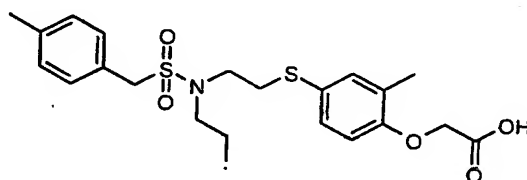
{2-Methyl-4-[2-(propyl-p-tolylmethanesulfonyl-amino)-ethylsulfanyl]-phenoxy}-acetic acid ethyl ester



To a cooled (0°C) solution of the trifluoroacetic acid salt of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (175 mg, 0.41 mmol) in methylene chloride (2 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 ml, 0.86 mmol) followed by p-tolyl-methanesulfonyl chloride (84 mg, 0.41 mmol). The mixture was stirred for 1 hour at 0°C, then stirred at room temperature for 20 hours. The mixture was diluted with methylene chloride (5 ml), then washed with 1N HCl, water and brine, and then dried (Na₂SO₄) and concentrated to an oil. The crude product was purified by silica chromatography to provide about 40 mg of the title compound (20%). MS (ES⁺) m/z: 480 (M+1).

Step B

{2-Methyl-4-[2-(propyl-p-tolylmethanesulfonyl-amino)-ethylsulfanyl]-phenoxy}-acetic acid



To a solution of {2-nethyl-4-[2-(propyl-p-tolylmethanesulfonyl-amino)-ethylsulfanyl]-phenoxy}-acetic acid ethyl ester (40 mg, 0.08 mmol) in methanol (2 ml) at

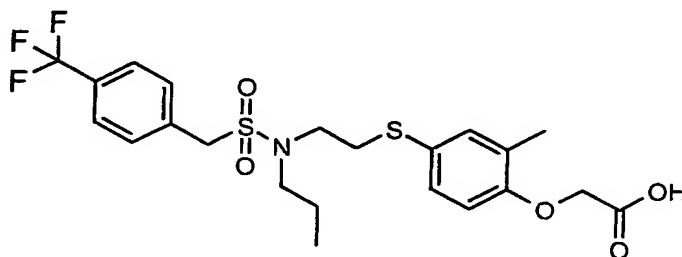
-246-

room temperature was added aqueous 5N NaOH (0.2 ml, 1 mmol), and the mixture was stirred for 18 hours. The mixture was concentrated to give a residue, which was dissolved in water (10 ml) and CH₂Cl₂ (15 ml). The mixture was adjusted to pH 4 with 6N HCl. After extracting the aqueous layer with CH₂Cl₂ (2 x 10 ml), the combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated to an oil, which was purified by preparative reverse-phase HPLC (elution with 1% TFA in acetonitrile) to afford about 34 mg (93%) of the title compound as a solid after lyophilization. MS (ES⁻) m/z: 450 (M-1).

The following Examples 185 to 193 were prepared according to the method as described in Example 184.

Example 185

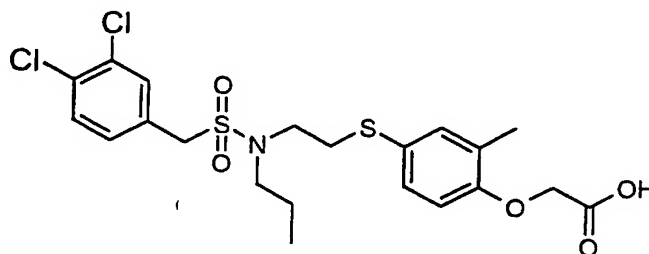
(2-Methyl-4-{2-[propyl-(4-trifluoromethyl)phenylmethanesulfonyl]-amino}-ethylsulfanyl}-phenoxy)-acetic acid



The title compound was prepared from (4-trifluoromethyl-phenyl)-methanesulfonyl chloride to afford 31 mg (15%). MS (ES⁻) m/z: 504 (M-1).

Example 186

(4-{2-[(3,4-Dichloro-phenylmethanesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

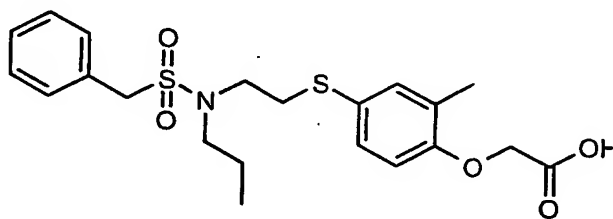


-247-

The title compound was prepared from (3,4-dichloro-phenyl)-methanesulfonyl chloride to afford 17 mg (8%). MS (ES⁻) m/z: 505 (M-1).

Example 187

5 {2-Methyl-4-[2-(phenylmethanesulfonyl-propyl-amino) ethylsulfanyl]-phenoxy}-acetic acid

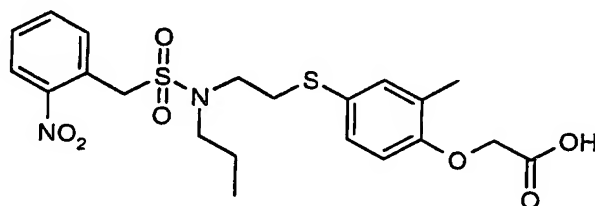


The title compound was prepared from phenyl-methanesulfonyl chloride to afford 24 mg (13%). MS (ES⁻) m/z: 436 (M-1).

10

Example 188

(2-Methyl-4-{2-[(2-nitro-phenylmethanesulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid



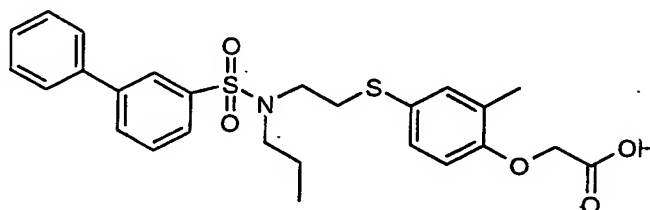
15

The title compound was prepared from (2-nitro-phenyl)-methanesulfonyl chloride to afford 12 mg (6%). MS (ES⁻) m/z: 481 (M-1).

-248-

Example 189

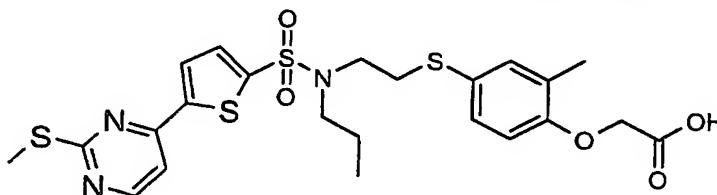
(4-{2-[(Biphenyl-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 The title compound was prepared from biphenyl-3-sulfonyl chloride to afford 30 mg (15%). MS (ES⁻) m/z: 498 (M-1).

Example 190

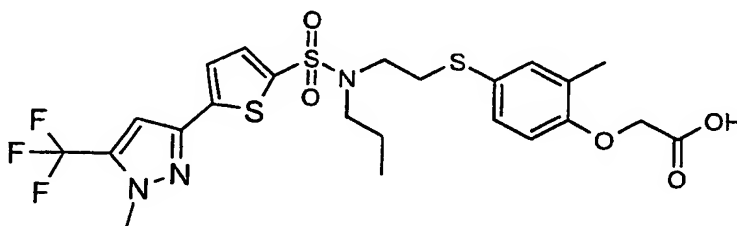
10 [2-Methyl-4-(2-{[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-propyl-amino}-ethylsulfanyl)-phenoxy]-acetic acid



The title compound was prepared from 5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl chloride to afford 39 mg (26%). MS (ES⁺) m/z: 554 (M+1).

Example 191

15 [2-Methyl-4-(2-{[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-propyl-amino}-ethylsulfanyl)-phenoxy]-acetic acid

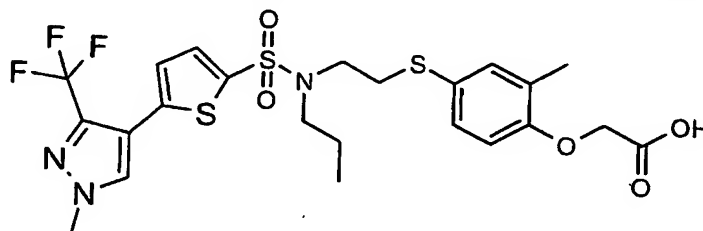


20 The title compound was prepared from 5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl chloride to afford 47 mg (30%). MS (ES⁺) m/z: 578 (M+1).

-249-

Example 192

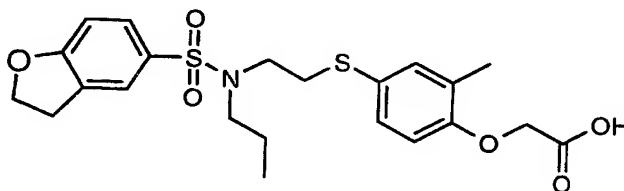
[2-Methyl-4-(2-{{5-(1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl}-propyl-amino}-ethylsulfanyl)-phenoxy]-acetic acid



5 The title compound was prepared from 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl chloride to afford 60 mg (38%). MS (ES⁺) m/z: 578 (M+1).

Example 193

10 (4-{2-[(2,3-Dihydro-benzofuran-5-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



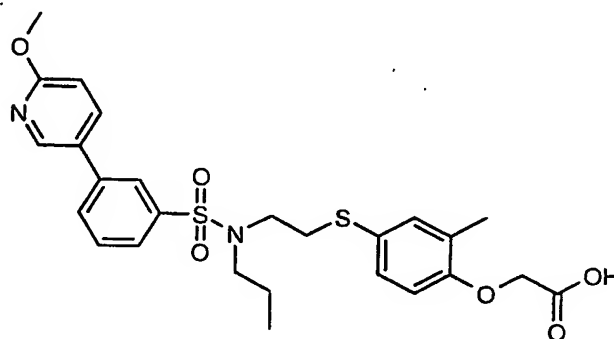
The title compound was prepared from 2,3-dihydro-benzofuran-5-sulfonyl chloride to afford 55 mg (44%). MS (ES⁻) m/z: 464 (M-1).

15

-250-

Example 194

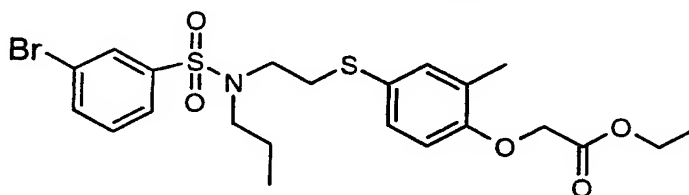
[4-(2-{[3-(6-Methoxy-pyridin-3-yl)-benzenesulfonyl]-propyl-amino}-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid



5

Step A

(4-{2-[(3-Bromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester.



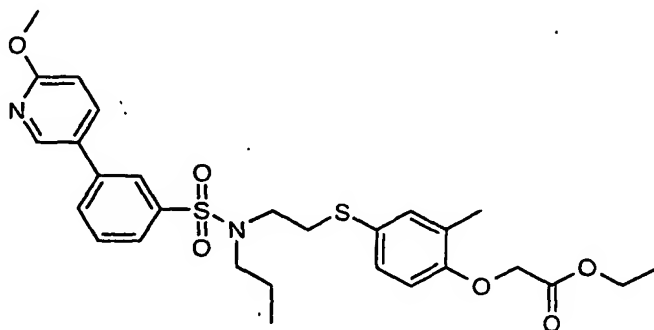
To a solution of the trifluoroacetic acid salt of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (429 mg, 1.37 mmol) in CH_2Cl_2 (6 ml) at 22°C was added triethylamine (0.77 ml, 5.5 mmol) followed by 3-bromo-benzenesulfonyl chloride (511 mg, 2.0 mmol) dropwise over two minutes. The mixture was stirred at room temperature for 18 hours, and then diluted with CH_2Cl_2 (20 ml) and 1N HCl (25 ml). After the aqueous layer was extracted with CH_2Cl_2 (10 ml), the organic layers were washed with water (20 ml), brine (20 ml), and then dried (Na_2SO_4) and concentrated to an oil which was purified by silica chromatography using 10:1 hexanes:ethyl acetate to provide about 510 mg as an oil (96%). MS (ES^+) m/z : 532 ($\text{M}+1$).

20

-251-

Step B

[4-(2-{[3-(6-Methoxy-pyridin-3-yl)-benzenesulfonyl]-propyl-amino}-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester.



To a solution of (4-{2-[(3-bromo-benzenesulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (125 mg, 0.23 mmol) in acetonitrile (2 ml) under N₂ at room temperature was added palladium acetate (6 mg, 0.023 mmol) followed by 2-methoxy-5-pyridine boronic acid (105 mg, 0.69 mmol), tricyclohexylphosphine (10 mg, 0.035 mmol), and cesium fluoride (314 mg, 2.07 mmol). The mixture was heated at 90° C for 6 hours, cooled to room temperature and concentrated to a solid. Purification by silica chromatography using 5:1 hexanes:acetone provided about 105 mg as a solid (82%). MS (ES⁺) m/z: 559 (M+1).

Step C

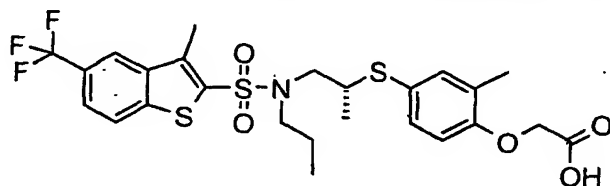
[4-(2-{[3-(6-Methoxy-pyridin-3-yl)-benzenesulfonyl]-propyl-amino}-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid

To a solution of [4-(2-{[3-(6-methoxy-pyridin-3-yl)-benzenesulfonyl]-propyl-amino}-ethylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (95 mg, 0.17 mmol) in methanol (2 ml) at room temperature was added aqueous 5N NaOH (0.10 ml, 0.5 mmol), and the mixture was stirred for 18 hours. The mixture was concentrated to give a residue, which was dissolved in water (10 ml) and CH₂Cl₂ (15 ml). The mixture was adjusted to pH 4 with 6N HCl. After extracting the aqueous layer with CH₂Cl₂ (2 x 10 ml), the combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated to provide about 75 mg of the title compound as a solid (83%). MS (ES⁺) m/z: 531 (M+1).

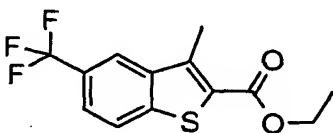
-252-

Example 195

(R)-(2-Methyl-4-{1-methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

Step A

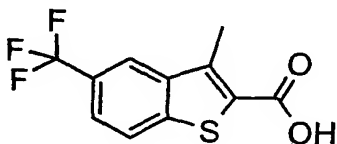
3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid ethyl ester.



To a solution of 2-fluoro-5-(trifluoromethyl)acetophenone (6.4 g, 31 mmol) and ethyl 2-mercaptoacetate (3.72 g, 31 mmol) in DMF (60 ml) was added cesium carbonate (20.2 g, 62 mmol), and the resulting mixture was heated at 80°C for 5 hours, which was then cooled to room temperature while stirring for 16 hours. The reaction mixture was diluted with water (600 ml) and extracted with diethyl ether (3 x 110 ml). The combined organic extracts were washed with brine (200 ml), dried (Na₂SO₄), and concentrated to provide the title compound as a solid, 8.16g (92%), which was used without further purification.

Step B

3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid.



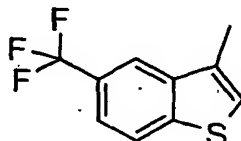
To a solution of 3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid ethyl ester (8.1 g, 28 mmol) in methanol (125 ml) at 45°C was added aqueous 5N NaOH (17 ml, 85 mmol), and the mixture was stirred for 6 hours while cooling to room temperature. The mixture was concentrated to give a residue, which was dissolved in water (100 ml) and ethyl acetate (150 ml). The mixture was adjusted to pH 3 with 1N HCl. After extracting the aqueous layer with ethyl acetate (2 x 40 ml), the

-253-

combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to provide the title compound as a solid, 7.1 g (97 %), which was used without further purification. MS (ES^-) m/z: 259 (M-1).

Step C

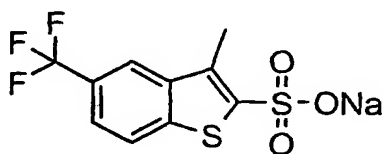
5 3-Methyl-5-trifluoromethyl-benzo[b]thiophene.



To a solution of 3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid (6.1 g, 23.4 mmol) in quinoline (200 ml) was added copper powder (0.89g, 14 mmol), and the mixture was heated at 200°C for one hour, which was then cooled to room temperature while stirring for 16 hours. The mixture was filtered through celite, and the filtrate was diluted with diethyl ether (300 ml). The filtrate was treated with ice (200 g). and the mixture was adjusted to pH 4 with concentrated hydrochloric acid. After extracting the aqueous layer with diethyl ether (2 x 100 ml), the combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated to an oil, which was purified by silica chromatography using hexanes to provide the title compound as a oil, 4.66 g (92%).

Step D

3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonic acid sodium salt



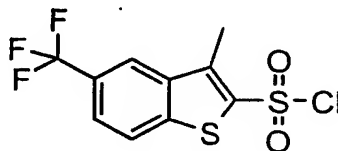
20 To a cooled solution of 3-methyl-5-trifluoromethyl-benzo[b]thiophene (3.83 g, 17.7 mmol) in trifluoroacetic acid (40 ml) at 5°C was added chlorosulfonic acid (1.2 ml, 17.7 mmol) dropwise over 5 minutes. The thick suspension was stirred for 5 minutes, warmed to 15°C and treated with additional chlorosulfonic acid (2.33 ml, 35.4 mmol) dropwise over 10 minutes. The mixture was stirred at 22°C for 2 hours, and then carefully poured into a mix of ice/water (375 g). After stirring for 15 minutes, the solution was filtered, and the filtrate extracted with diethyl ether (6 x 100 ml). To the combined ether extracts was added brine (250 ml). which affected the precipitation of a

-254-

solid. The resulting suspension was filtered to give the title compound as a solid, 2.8 g, after drying. The filtrate was again extracted with ethyl ether (200 ml), and the organic extract was treated with brine (120 ml). Subsequent filtration and drying afforded about 1.3 g of the title compound, which was used without further purification. The combined
5 yield was 73%. MS (ES⁻) m/z: 295 (M-1).

Step E

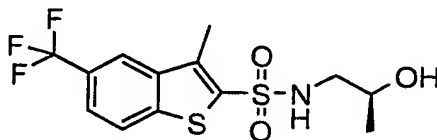
3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl chloride.



To a suspension of 3-Methyl-5-trifluoromethylbenzo[b]thiophene-2-sulfonic acid sodium salt (2.14 g, 6.72 mmol) in chloroform (12 ml) at room temperature
10 was added chlorosulfonic acid (1.34 ml, 20.2 mmol) dropwise over 10 minutes. The resulting suspension was heated at 60°C for 4.5 hours, cooled to room temperature and carefully poured into a mix of ice/water (250 g). The mixture was extracted with chloroform (3 x 20 ml), and the combined organic extracts were washed with cold water
15 (0°C), dried (Na₂SO₄), and concentrated to provide the title compound as a solid, 1.45 g (69 %), which was used without further purification.

Step F

(S)-3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide.



20

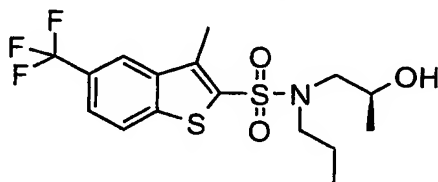
To a cooled solution of (S)-1-amino-propan-2-ol (0.34 g, 4.6 mmol) in methylene chloride (3 ml) at 0°C was added triethylamine (1.92 ml, 13.8 mmol) followed by a dropwise addition of a solution of 3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl chloride (1.45 g, 4.6 mmol) in methylene chloride (15 ml) over 3 minutes. The
25 mixture was removed from the cooling bath and stirred for 1.5 hours, which was then diluted with 1N HCl (50 ml) and methylene chloride (20 ml). The aqueous layer was extracted with methylene chloride (20 ml), and the combined organic layers were washed

-255-

with brine (40 ml), dried (Na_2SO_4), and concentrated to provide the title compound as a solid, 1.51 g (92 %) which was used without further purification. MS (ES^+) m/z : 354 ($M+1$).

Step G

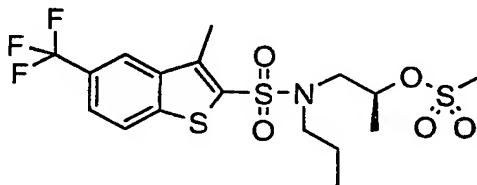
- 5 (S)-3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide.



- To a solution of (S)-3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide (1.5 g, 4.24 mmol) in N,N -dimethylformamide (15 ml) at room temperature was added n-propyl iodide (0.49 ml, 5.0 mmol) followed by cesium carbonate (1.65 g, 5 mmol), and the resulting mixture stirred for 18 hours. The mixture was diluted with water (120 ml) and ethyl acetate (70 ml), and the aqueous layer was extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with water (100 ml), brine (120 ml), dried (Na_2SO_4), and concentrated to a solid.
- 15 Purification by silica chromatography using 4:1 hexanes:acetone provided the title compound as a solid, 1.49 g (89%). MS (ES^+) m/z : 396 ($M+1$).

Step H

- (S)-Methanesulfonic acid 1-methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester.



20

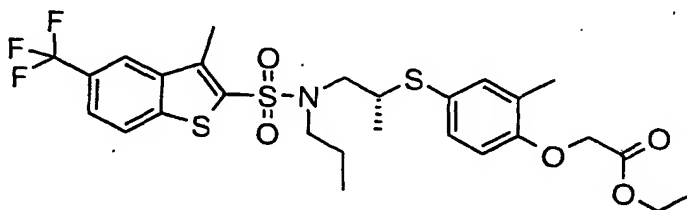
- To a cooled (0°C) solution of (S)-3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (1.0 g, 2.52mmol) and triethylamine (0.53 ml, 3.78 mmol) in methylene chloride (11 ml) was added methanesulfonyl chloride (0.23 ml, 3 mmol) dropwise over 2 minutes. The mixture was stirred at 0°C for 2 hours, diluted with additional methylene chloride (25 ml), and then washed with 1N HCl (50 ml). The aqueous layer was back-extracted with methylene
- 25

-256-

chloride (2 x 20 ml), and the combined organic extracts were washed with brine (75 ml), dried (Na_2SO_4), and concentrated to afford the title compound as an oil, 1.1 g (100%), which was used without further purification. MS (ES^+) m/z : 474 ($\text{M}+1$).

Step I

- 5 (R)-(2-Methyl-4-{1-methyl-2-[(3-methyl-5-trifluoromethyl)-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester



- A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.57g, 2.51 mmol) in N,N-dimethylformamide (12 ml) at room temperature was purged with N_2 gas, and potassium carbonate (520 mg, 3.76 mmol) was added followed by a solution of (S)-methanesulfonic acid 1-methyl-2-[(3-methyl-5-trifluoromethyl)-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (1.19 g, 2.51 mmol) in N,N-dimethylformamide (7 ml) dropwise over 2 minutes. The mixture was stirred at room temperature for 24 hours, diluted with diethyl ether (50 ml), and washed with 1N HCl (2 x 25 ml) and brine (60 ml), and then dried (Na_2SO_4). Concentration in vacuo produced a crude oil, which was purified by silica chromatography using 8:1 hexanes:ethyl acetate to afford the title compound as a oil, 0.79 g (52%). MS (ES^+) m/z : 604 ($\text{M}+1$).

Step J

- 20 (R)-(2-Methyl-4-{1-methyl-2-[(3-methyl-5-trifluoromethyl)-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

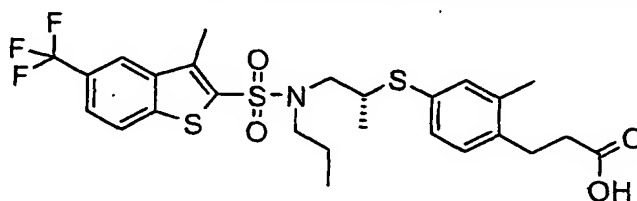
- To a solution of (R)-(2-methyl-4-{1-methyl-2-[(3-methyl-5-trifluoromethyl)-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester (790 mg, 1.30 mmol) in ethanol (10 ml) at room temperature was added aqueous 5N NaOH (1.3 ml, 6.5 mmol), and the mixture was stirred for 3 hours. The mixture was concentrated to give a residue, which was dissolved in water (50 ml) and ethyl acetate (70 ml), and the mixture was adjusted to pH 3 with 1N HCl. After extracting the aqueous layer with ethyl acetate (20 ml), the combined organic extracts were washed

-257-

with water (40 ml) and brine (50 ml), dried (Na_2SO_4) and concentrated to provide the title compound as a foam, 710 mg (95%). MS (ES^-) m/z : 574 ($\text{M}-1$).

Example 196

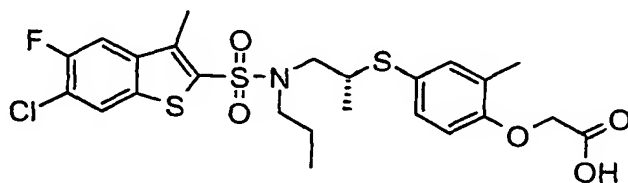
5 (R)-3-(2-Methyl-4-{1-methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenyl)-propionic acid



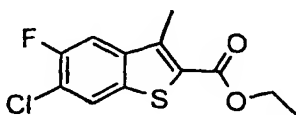
Using the method as described in Example 195, (S)-methanesulfonic acid 1-methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (Example 21, Step H) and 3-(4-mercapto-2-methyl-phenyl)-propionic acid methyl ester afforded the title compound. MS (ES^-) m/z : 572 ($\text{M}-1$).

Example 197

15 (R)-(4-{2-[(6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-carboxylic acid ethyl ester.



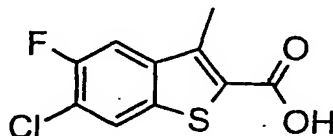
20 To a solution of 1-(4-chloro-2,5-difluoro-phenyl)-ethanone (4.9 g, 25.7 mmol) and ethyl 2-mercaptoacetate (2.81 g, 23.4 mmol) in DMF (50 ml) was added cesium carbonate (15.2 g, 46.8 mmol) and the resulting mixture was heated at 80°C for 5 hours, and then cooled to room temperature while stirring for 16 hours. The reaction mixture was diluted with water (500 ml) and extracted with diethyl ether (2 x 100 ml).

-258-

The combined organic extracts were washed with brine (200 ml), dried (Na_2SO_4), and concentrated to give an oil which was purified by silica chromatography using 8:1 hexanes:ethyl acetate to afford the title compound as a solid, 1.4 g (22%).

Step B

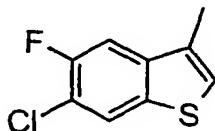
5 6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-carboxylic acid



To a solution of 6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-carboxylic acid ethyl ester (3.3 g, 12.2 mmol) in ethanol (110 ml) at room temperature was added aqueous 5N NaOH (7.3 ml, 36.6 mmol), and the mixture was stirred for 24
10 hours. The mixture was concentrated to give a residue, which was suspended in water (50 ml) and ethyl acetate (75 ml), which was then adjusted to pH 3 with 6N HCl. The suspension was filtered and the filtered solid was washed with ethyl acetate, and dried to afford the title compound as a solid, 1.3 g. A second crop was obtained from the filtrate after extracting the aqueous layer with ethyl acetate (3 x 40 ml), and then the combined
15 organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to provide the title compound as a solid, 1.1 g (77 % combined yield) which was used without further purification. MS (ES^-) m/z: 243 (M-1).

Step C

6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene.



20

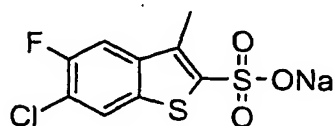
To a solution of 6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-carboxylic acid (2.3 g, 9.4 mmol) in quinoline (55 ml) was added copper powder (0.36 g, 5.64 mmol), and the mixture was heated at 200°C for 40 minutes and cooled to room temperature. The reaction mixture was diluted with diethyl ether (70 ml) and filtered
25 through celite. The filtrate was washed with 5N HCl (4 x 100 ml), water (100 ml) and brine (150 ml), and then dried (Na_2SO_4) and concentrated to an oil, which was purified by

-259-

silica chromatography using hexanes to provide the title compound as a solid, 1.64 g (92%). HRMS (EI⁺) m/z exact mass calculated for C₉H₆ClFS 199.9863, found 199.9836.

Step D

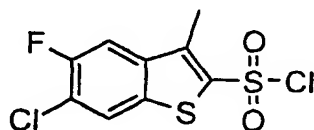
6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonate sodium salt



To a cooled solution of 6-chloro-5-fluoro-3-methyl-benzo[b]thiophene (1.43 g, 7.1 mmol) in trifluoroacetic acid (3 ml) and 1,2-dichloroethane (3 ml) at 5°C was added chlorosulfonic acid (0.47 ml, 7.1 mmol) dropwise over 10 minutes. The thick suspension was stirred for 5 minutes, warmed to 15° C and treated with additional chlorosulfonic acid (0.95 ml, 14.2 mmol) dropwise over 10 minutes. The mixture was stirred at room temperature for 5 hours, and then carefully poured into a mix of ice/water (300 g). After stirring for 10 minutes, the mixture was extracted with chloroform (3 x 50 ml). The aqueous layer was diluted with brine (350 ml), which affected the precipitation of a solid over the course of 2 days. The resulting suspension was filtered, and the filtered solid was dried to give the title compound as a solid, 0.97 g (45%), which was used without further purification. MS (ES⁻) m/z: 279 (M-1).

Step E

6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride

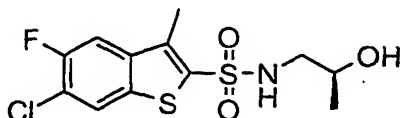


To a suspension of 6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonate sodium salt (1.44 g, 4.75 mmol) in chloroform (12 ml) at room temperature was added chlorosulfonic acid (0.94 ml, 14.3 mmol) dropwise over 10 minutes. The resulting suspension was heated at 55°C for 3.5 hours, cooled to room temperature, diluted with chloroform (35 ml), and carefully poured into a mix of ice/water (200 g). The mixture was extracted with chloroform (3 x 20 ml), and the combined organic extracts were washed with cold water (0°C) (3 x 75 ml), dried (Na₂SO₄) and concentrated to provide the title compound as a solid, 1 g (70 %) which was used without further purification.

-260-

Step F

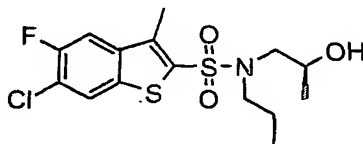
(S)-6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide



To a cooled solution of (S)-1-amino-propan-2-ol (0.25 g, 3.34 mmol) in methylene chloride (2 ml) at 0°C was added triethylamine (1.4 ml, 10 mmol) followed by dropwise addition of a solution of 6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (1 g, 3.34 mmol) in methylene chloride (10 ml) over 10 minutes. The mixture was removed from the cooling bath and stirred for 18 hours, and then diluted with 1N HCl (50 ml) and methylene chloride (35 ml). The resulting suspension was filtered to provide the title compound as a solid, 0.8 g (71 %), which was used without further purification. MS (ES⁺) m/z: 338 (M+1).

Step G

(S)-6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide

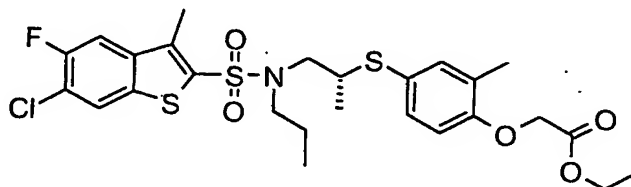


To a solution of (S)-6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-amide (0.79 g, 2.36 mmol) in N,N-dimethylformamide (6 ml) at room temperature was added n-propyl iodide (0.27 ml, 2.83 mmol) followed by cesium carbonate (922 mg, 2.83 mmol), and the resulting mixture was stirred for 18 hours. The mixture was diluted with 1N HCl (50 ml) and ethyl acetate (25 ml), and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with water (40 ml) and brine (40 ml), and then dried (Na₂SO₄) and concentrated to a solid, which was purified by silica chromatography using 3:1 hexanes:ethyl acetate to provide the title compound as a solid, 0.87 g (98%). MS (ES⁺) m/z: 381 (M+1).

-261-

Step H

(R)-(4-{2-[(6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



5 To a cooled solution of (S)-6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (299 mg, 0.78 mmol) and (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester 2064321 (176 mg, 0.78 mmol) in toluene (4 ml) at 0°C was added tri-n-butylphosphine (0.23 ml, 0.94 mmol) over 2 minutes followed by the dropwise addition of a solution of 1,1'-
10 (azodicarbonyl)dipiperidine (237 mg, 0.94 mmol) in toluene (4 ml) over 5 minutes. The suspension was stirred in an ice bath for 18 hours. The mixture was filtered, and the filtrate was concentrated to give an oil. Purification by silica chromatography using 8:1 hexanes:ethyl acetate provided the title compound as an oil, 338 mg (74%). MS (ES⁺) m/z: 588 (M+1).

15

Step I

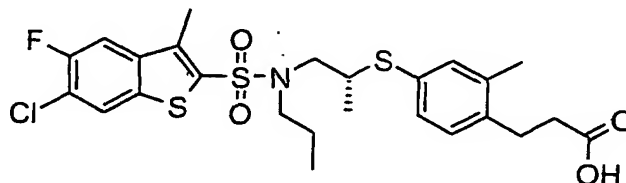
(R)-(4-{2-[(6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

To a solution of (R)-(4-{2-[(6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-
20 phenoxy)-acetic acid ethyl ester (334 mg, 0.56 mmol) in methanol (40 ml) at 45°C was added aqueous 5N NaOH (2 ml, 10 mmol), and the mixture was stirred for 18 hours while cooling to room temperature. The mixture was concentrated to give a residue, which was dissolved in water (40 ml) and ethyl acetate (30 ml), and the mixture was adjusted to pH 3 with 5N HCl. After extracting the aqueous layer with ethyl acetate (20 ml), the combined
25 organic extracts were washed with water (100 ml) and brine (100 ml), and then dried (Na₂SO₄) and concentrated to provide the title compound as a solid, 293 mg (94%). MS (ES⁻) m/z: 558 (M-1).

-262-

Example 198

(R)-3-(4-{2-[(6-Chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenyl)-propionic acid

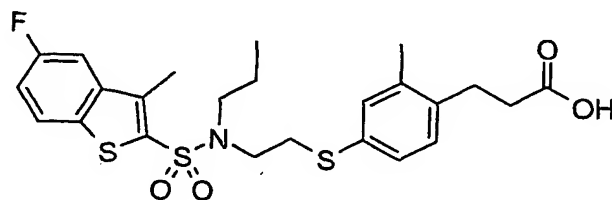


5 Using the method as described in Example 197, (S)-6-chloro-5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (Example 23, Step G) and 3-(4-mercapto-2-methyl-phenyl)-propionic acid methyl ester afforded the title compound. MS (ES⁻) m/z: 556 (M-1).

10

Example 199

3-(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid



Sodium hydride (60% in mineral oil; about 30 mg, about 18 mg NaH, about 0.75 mmol) was added to a solution of 3-(4-mercapto-2-methyl-phenyl)-propionic acid methyl ester (50 mg, 0.24 mmol) in anhydrous DMF (2 mL). After stirring for about 15 min, toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (97 mg, 0.20 mmol, 1 equiv) was added followed by additional anhydrous DMF (2 mL) to rinse. The mixture was stirred for 3 hours and then quenched with 1 M aq HCl (6 mL). The mixture was extracted with Et₂O (2 x 5 mL), dried with anhydrous MgSO₄, and evaporated (50°C) to give 97 mg of crude methyl ester as a yellow oil, which was eluted (50 mL 5% EtOAc/hex, 100 mL 10% EtOAc/hex) through a chromatotron (1 mm plate) yielding 42 mg of the purified methyl ester. This material was dissolved in EtOH (4 mL) and 5 M aq NaOH (0.4 mL) and rotary evaporated. The resultant residue was acidified with 5 M aq HCl (2 mL) and then

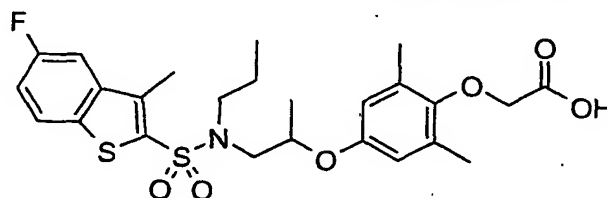
-263-

extracted with CH_2Cl_2 (5 mL). The organic layer was dried (anhydrous MgSO_4) and rotary evaporated (50°C) to yield 30 mg (29%) of the acid as a yellow oil. Calculated for $\text{C}_{24}\text{H}_{28}\text{FNO}_4\text{S}_3$: m/z 510.1243. Found: 510.1241

5

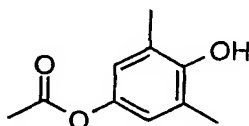
Example 200

(4-{2-[(5-Fluoro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methoxy}-2,6-dimethyl-phenoxy)-acetic acid

Step A

10

Acetic acid 4-hydroxy-3,5-dimethyl-phenyl ester

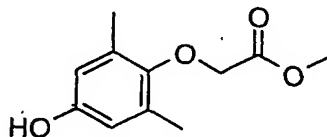


Acetic anhydride (1.5 mL, 1.6 g, 16 mmol, 1.1 equiv) was added dropwise over a period of 3 min to a hazy solution of 2,6-dimethylhydroquinone (2.00 g, 14.5 mmol, 1 equiv) and diisopropylethylamine (2.8 mL, 2.1 g, 16 mmol, 1.1 equiv) in CH_2Cl_2 (80 mL). Within 5 min after the addition, the reaction solution was completely clear. After stirring for about 18 h, the solution was evaporated (50°C) to give 4.57 g of a brown oil, which was then take up in Et_2O (80 mL), washed with 0.2 M aq HCl (2 x 40 mL), dried (anhydrous Na_2SO_4), and rotary evaporated (50°C) to afford about 2.43 g of a red-brown oil. The oil was eluted (100 mL 10% EtOAc/hex, 200 mL 20% EtOAc/hex, 200 mL 30% EtOAc/hex) through a chromatotron (6 mm plate) yielding 1.31 g (50.2%) of product as a yellow crystalline solid.

-264-

Step B

(4-Hydroxy-2,6-dimethyl-phenoxy)-acetic acid methyl ester



Potassium carbonate (220 mg, 1.6 mmol, 3.0 equiv) was added to a
5 solution of acetic acid 4-hydroxy-3,5-dimethyl-phenyl ester (96 mg, 0.53 mmol, 1 equiv)
in anhydrous DMF (5 mL) followed by *tert*-butyl bromoacetate (100 μ L, 130 mg,
0.68 mmol, 1.3 equiv). The mixture was stirred at 80°C for 2 h, which was then poured
into H₂O (25 mL) and extracted with EtOAc (10 mL). The organic layer was washed
with H₂O (2 x 5 mL), dried (anhydrous MgSO₄), and rotary evaporated (75 °C) giving
10 127 mg (81%) of phenylacetate intermediate as an orange-brown oil. The oil was
dissolved in EtOH (2 mL) and 5 M aq NaOH (2 mL) was added. The mixture was rotary
evaporated, acidified with 1 M aq HCl (10 mL), and extracted with EtOAc (2 x 5 mL).
The combined organic layers were dried (anhydrous MgSO₄) and rotary evaporated to
afford 64 mg (61%) of phenol acid as a brown crystalline solid, which was dissolved in
15 CH₂Cl₂ (2 mL) and MeOH (0.5 mL) and (trimethylsilyl)diazomethane (2.0 M in
hexanes; 0.5 mL) was added. After stirring for 5 min, the mixture was evaporated (50 °C;
azeotrope 2x with CH₂Cl₂) to give about 67 mg (60%) of methyl ester phenol as a brown
oil. Calculated for C₂₅H₃₀FNO₆S₂: m/z 210.0892. Found: 210.0884

Step C

20 (4-{2-[(5-Fluoro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-
ethoxy}-2,6-dimethyl-phenoxy)-acetic acid

Cesium carbonate (260 mg, 0.80 mmol, 3.0 equiv) was added to a solution
of (4-hydroxy-2,6-dimethyl-phenoxy)-acetic acid methyl ester (56 mg, 0.27 mmol,
1.0 equiv) and toluene-4-sulfonic acid 2-[(5-fluoro-3-methyl-benzo[*b*]thiophene-2-
25 sulfonyl)-propyl-amino]-1-methyl-ethyl ester (133 mg, 0.27 mmol, 1 equiv) in anhydrous
DMF (3 mL). The mixture was stirred at 50°C for 16 h, which was poured into H₂O
(15 mL) and extracted with Et₂O (10 mL). The organic layer was dried (anhydrous
MgSO₄) and evaporated (50°C) giving 111 mg of crude methyl ester as a yellow oil. The
oil was eluted (100 mL 5% EtOAc/hex, 100 mL 10% EtOAc/hex, 100 mL 20%

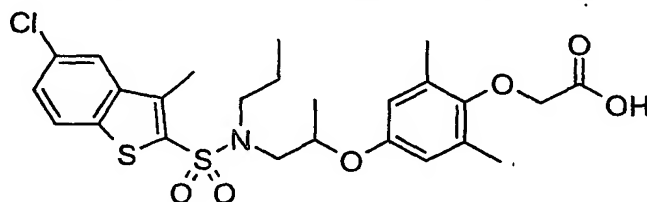
-265-

EtOAc/hex) through a chromatotron (1 mm plate) to yield 18 mg of the purified methyl ester, which was then dissolved in EtOH (2 mL) and 5 M aq NaOH (0.2 mL). The solution was evaporated, acidified with 5 M aq HCl (2 mL), and then extracted with CH₂Cl₂ (5 mL). The organic layer was dried (anhydrous MgSO₄) and evaporated (50°C) to afford about 12 mg (8.6%) of the acid as a colorless oil.

Calculated for C₂₅H₃₀FNO₆S₂: m/z 546.1396. Found: 546.1403

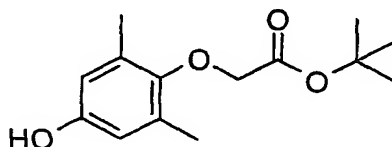
Example 201

(4-{2-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methylethoxy}-2,6-dimethyl-phenoxy)-acetic acid



Step A

(4-Hydroxy-2,6-dimethyl-phenoxy)-acetic acid *tert*-butyl ester



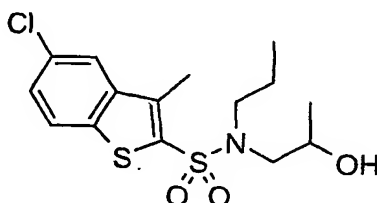
Potassium carbonate (2.7 g, 20 mmol, 3.0 equiv) was added to a solution of acetic acid 4-hydroxy-3,5-dimethyl-phenyl ester (1.19 g, 6.60 mmol, 1 equiv) in anhydrous DMF (60 mL) followed by *tert*-butyl bromoacetate (1.0 mL, 1.3 g, 6.8 mmol, 1.3 equiv). The mixture was stirred at 80°C for 2 h and then at 20°C for 14 h, which was poured into H₂O (300 mL) and extracted with EtOAc (100 mL). The organic layer was washed with H₂O (2 x 50 mL), dried (anhydrous Na₂SO₄), and rotary evaporated (75°C) giving 1.63 g (84%) of phenylacetate intermediate as an orange-brown oil. The oil was dissolved in 10% *N,N*-diisopropylethyamine in MeOH (80 mL) and stirred for 4 h. The solution was evaporated to give a brown oil, which was dissolved in Et₂O (50 mL) and washed with 1 M aq HCl (25 mL). The organic layer was dried (anhydrous Na₂SO₄) and rotary evaporated (65°C) giving 1.27 g (76%) of crude product as a brown oil. The oil was eluted (100 mL 10% EtOAc/hex. 400 mL 20% EtOAc/hex) through a chromatotron

-266-

(4 mm plate) yielding 263 mg (16%) of the pure compound as a cream-colored crystalline solid and another 382 mg of less-pure material.

Step B

5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide

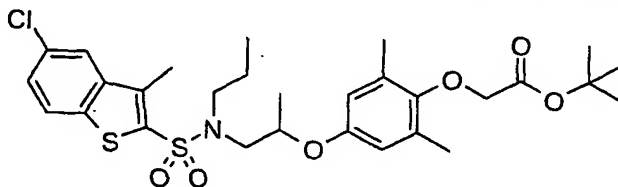


5 The compound of 5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl chloride (1.35 g, 4.80 mmol, 1 equiv) in one portion was added to a solution of 1-amino-2-propanol (0.45 mL, 0.44 g, 5.8 mmol, 1.2 equiv) and triethylamine (1.4 mL, 1.0 g, 10 mmol, 2.1 equiv) in anhydrous CH₂Cl₂ (50 mL) cooled to 0°C. After stirring for 2 h, 10 the solution was washed with 1 M aq HCl (25 mL), dried (anhydrous Na₂SO₄), and rotary evaporated (50°C) giving 1.46 g (95%) of the secondary amide as an off-white solid. The solid was dissolved in anhydrous DMF (30 mL), and cesium carbonate (2.0 g, 6.1 mmol, 1.3 equiv) was added followed by 1-iodopropane (0.62 mL, 1.1 g, 6.4 mmol, 1.3 equiv). The mixture was stirred at 50°C. After 1 h, the mixture was poured into 1 M aq HCl 15 (60 mL) and extracted with Et₂O (60 mL). The organic layer was dried (anhydrous Na₂SO₄) and rotary evaporated (50°C) to afford about 1.58 g (91%) of tertiary amide as a yellow crystalline solid. The solid was eluted (100 mL 20% EtOAc/hex, 100 mL 30% EtOAc/hex, 100 mL 40% EtOAc/hex, 150 mL 50% EtOAc/hex) through a chromatotron (4 mm plate) yielding 1.35 g (78%) of the purified material as an off-white crystalline 20 solid.

-267-

Step C

(4-{2-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2,6-dimethyl-phenoxy)-acetic acid *tert*-butyl ester



5 The compound of diisopropyl azodicarboxylate (50 μ L, 51 mg, 0.25 mmol, 1.0 equiv) was added over a period of 1 min to a solution of (4-hydroxy-2,6-dimethyl-phenoxy)-acetic acid *tert*-butyl ester (63 mg, 0.25 mmol, 1 equiv), 5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (90 mg, 0.25 mmol, 1.0 equiv), and triphenylphosphine (66 mg, 0.25 mmol, 1.0 equiv) in toluene
10 (3 mL). The reaction solution was stirred for 16 h. and rotary evaporated. The resultant yellow oil was eluted (100 mL 5% EtOAc/hex, 150 mL 10% EtOAc/hex) through a chromatotron (1 mm plate) yielding 100 mg (67%) of the desired product as a colorless oil. Calculated for $C_{29}H_{38}ClNNaO_6S_2$: m/z 618.1727. Found: 618.1713

Step D

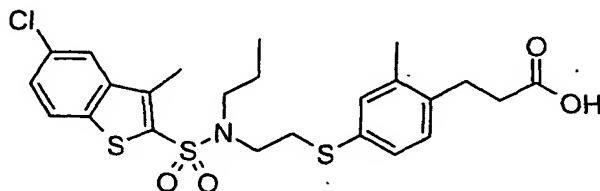
15 (4-{2-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2,6-dimethyl-phenoxy)-acetic acid

 The compound of (4-{2-[(5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2,6-dimethyl-phenoxy)-acetic acid *tert*-butyl ester (100 mg, 0.168 mmol) was dissolved in 4 M HCl in 1,4-dioxane (5 mL), and the
20 mixture was stirred for 17 h and then rotary evaporated (50°C; azeotrope with CH_2Cl_2) yielding 96 mg (100%) to give the title compound as an off-white foam. Calculated for $C_{25}H_{30}ClNO_6S_2$: m/z 540.1281. Found: 540.1290.

-268-

Example 202

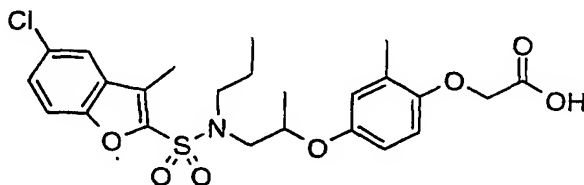
3-(4-{2-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid



- 5 A mixture of 3-(4-mercapto-2-methyl-phenyl)-propionic acid methyl ester (53 mg, 0.25 mmol, 1 equiv), toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (127 mg, 0.25 mmol, 1.0 equiv), and cesium carbonate (250 mg, 0.77 mmol, 3.0 equiv) in anhydrous DMF (5 mL) was stirred at 60°C for 13 h. The mixture was poured into H₂O (30 mL) and extracted with
- 10 Et₂O (3 x 15 mL). The organic layer was dried (anhydrous MgSO₄) and rotary evaporated (50°C) giving 68 mg of a yellow oil, which was then dissolved in EtOH (5 mL) and 5 M aq NaOH (0.5 mL). After 15 h, the solution was rotary evaporated, acidified with 5 M aq HCl (2 mL) and extracted with CH₂Cl₂ (5 mL). The organic layer was dried (anhydrous MgSO₄) and rotary evaporated (50°C) yielding 99 mg of the crude
- 15 acid as a yellow oil, which was purified by reverse-phase chromatography to afford about 25 mg (19%) of the acid as a white crystalline solid. Calculated for C₂₄H₂₈ClNNaO₄S₃: m/z 548.0767. Found: 548.0767.

Example 203

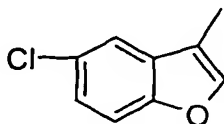
20 (4-{2-[(5-Chloro-3-methyl-benzofuran-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid



-269-

Step A

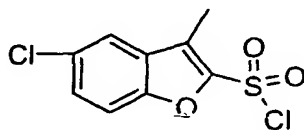
5-Chloro-3-methyl-benzofuran



2-Acetyl-4-chlorophenoxy acetic acid (2.06g, 9.0 mmol) and NaOAc (4.43g, 54 mmol) was added to Ac₂O (45.0 mL) and the mixture was heated at 110°C under N₂ for 3 hours. The mixture was cooled to ambient temperature and poured into H₂O (200mL) and stirred overnight. The aqueous mixture was extracted with Et₂O (450 mL) and the Et₂O layer was separated. The Et₂O was extracted with H₂O (5X 100mL), washed with brine and dried (MgSO₄) and filtered. The filtrate was evaporated and the resulting oil was chromatographed on the chromatron using a 4mm plate and eluted with EtOAc/hexane (5:95) to give about 0.98g(65%). NMR CDCl₃ δ 7.45 (m, 1H), 7.42 (m, 1H), 7.38(d, 1H), 7.25 (m, 1H), 2.22(S, 3H).

Step B

5-Chloro-3-methyl-benzofuran-2-sulfonyl chloride

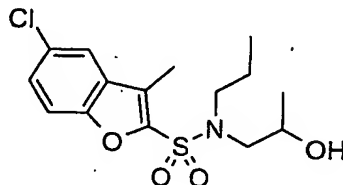


n-BuLi 2.5 M (1.20 mL, 3.0 mmol) was added to 5-chloro-3-methyl-benzofuran (0.40g, 2.40 mmol) in dry THF (4.0 mL) under N₂ at -5°C over 15 minutes. The light brown solution was stirred for 30 minutes at -5°C to 0°C. This mixture was added by syringe to a stirring solution of SO₂Cl₂ (0.23 mL, 2.9 mmol) in hexane (4.0 mL) at -5°C to 0°C and stirred for 1 hour. The mixture was warmed to ambient temperature and diluted with H₂O (10 mL), neutralized with solid NaHCO₃ and diluted with hexane (60mL). The organic layer was separated and dried (MgSO₄), filtered and evaporated on the rotary to viscous oil. Chromatography on the chromatotron eluting with EtOAc-hexane 5:95 gave an oil 0.67g. NMR CDCl₃ δ 7.70-7.758 (m, 3H), 2.62(S, 3H).

-270-

Step C

5-Chloro-3-methyl-benzofuran-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide



A solution of 5-chloro-3-methyl-benzofuran-2-sulfonyl chloride (268 mg, 1.01 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) was added to a solution of 1-amino-2-propanol (95 μL , 92 mg, 1.2 mmol, 1.2 equiv) and triethylamine (280 μL , 200 mg, 2.0 mmol, 2.0 equiv) in anhydrous CH_2Cl_2 (5 mL) cooled to 0°C . After stirring for 30 min, the solution was washed with 1 M aq HCl (5 mL), dried (anhydrous MgSO_4), and rotary evaporated (50°C) giving 242 mg (79%) of the secondary amide as a light-yellow crystalline solid, which was then dissolved in anhydrous DMF (5 mL). Cesium carbonate (430 mg, 1.3 mmol, 1.3 equiv) was added to the solution followed by 1-iodopropane (130 μL , 230 mg, 1.3 mmol, 1.3 equiv). The mixture was stirred at 50°C , and after 1 h, it was poured into 1 M aq HCl (25 mL) and extracted with Et_2O (25 mL). The organic layer was dried (anhydrous MgSO_4) and rotary evaporated (50°C) giving 246 mg (70%) of tertiary amide as a light-yellow crystalline solid. The solid was eluted (150 mL 30% EtOAc/hex) through a chromatotron (1 mm plate) yielding 154 mg (44%) of the purified material as a white crystalline solid.

Calculated for $\text{C}_{15}\text{H}_{20}\text{ClNNaO}_4\text{S}$: m/z 368.0699. Found: 368.0701.

Step D

(4-{2-[(5-Chloro-3-methyl-benzofuran-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid

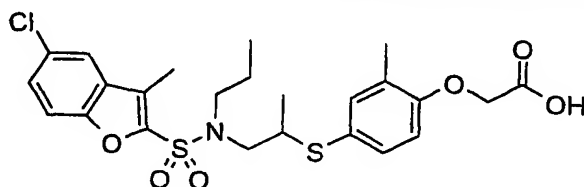
Diisopropyl azodicarboxylate (26 μL , 27 mg, 0.13 mmol, 1.0 equiv) over a period of 1 min was added to a solution of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (26 mg, 0.13 mmol, 1 equiv), 5-chloro-3-methyl-benzofuran-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (46 mg, 0.13 mmol, 1.0 equiv), and triphenylphosphine (35 mg, 0.13 mmol, 1.0 equiv) in anhydrous toluene (3 mL). The solution was stirred for 22 h, and the mixture was rotary evaporated. The resultant yellow oil was eluted (200 mL 5% EtOAc/hex, 200 mL 10% EtOAc/hex) through a chromatotron (1 mm plate) yielding

-271-

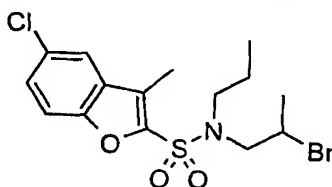
40 mg (58%) of the methyl ester as a colorless oil, which was dissolved in EtOH (4 mL) and 5 M aq NaOH (0.4 mL). After stirring 15 h, the solution was rotary evaporated, the residue was acidified with 5 M aq HCl (2 mL) and then extracted with CH₂Cl₂ (5 mL). The organic layer was dried (anhydrous MgSO₄) and rotary evaporated (50 °C) to afford about 32 mg (47%) of the acid as a colorless oil. Calculated for C₂₄H₂₈ClNNaO₇S: m/z 532.1173. Found: 532.1160.

Example 204

(4-{2-[(5-Chloro-3-methyl-benzofuran-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

5-Chloro-3-methyl-benzofuran-2-sulfonic acid (2-bromo-propyl)-propyl-amide



Triphenylphosphine (93 mg, 0.35 mmol, 1.5 equiv) was added to a solution of 5-chloro-3-methyl-benzofuran-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (82 mg, 0.24 mmol, 1 equiv) and carbon tetrabromide (120 mg, 0.36 mmol, 1.5 equiv) in dichloromethane (3 mL). The solution was stirred for 21 hours and rotary evaporated, and the resultant yellow oil was eluted (200 mL 5% EtOAc/hex) through a chromatotron (1 mm plate) to afford about 79 mg (82%) of the product as a white crystalline solid. Calculated for C₁₅H₂₀ClNNaO₄S: m/z 368.0699. Found: 368.0701.

Step B

(4-{2-[(5-Chloro-3-methyl-benzofuran-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

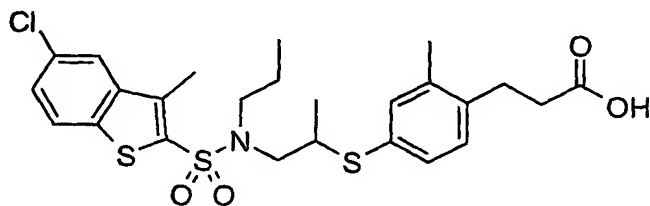
A mixture of 5-chloro-3-methyl-benzofuran-2-sulfonic acid (2-bromo-propyl)-propyl-amide (48 mg, 0.12 mmol, 1 equiv), (4-mercapto-2-methyl-phenoxy)-

-272-

acetic acid ethyl ester (27 mg, 0.12 mmol, 1.0 equiv), and cesium carbonate (110 mg, 0.34 mmol, 2.9 equiv) in anhydrous DMF (5 mL) was stirred at 60°C for 18 h. The mixture was poured into H₂O (30 mL) and extracted with Et₂O (4 x 15 mL). The organic layer was dried (anhydrous MgSO₄) and rotary evaporated (50 °C) giving 58 mg of a yellow oil, which was eluted (100 mL 5% EtOAc/hex, 100 mL 10% EtOAc/hex) through a chromatotron (1 mm plate) yielding 11 mg of the ethyl ester as a colorless film. The material was dissolved in EtOH (1 mL) and 5 M aq NaOH (0.1 mL). After stirring 16 h, the solution was evaporated. The resultant residue was acidified with 1 M aq HCl (2 mL) and then extracted with CH₂Cl₂ (5 mL). Dry the organic layer was dried (anhydrous MgSO₄) and rotary evaporated (50°C) to yield about 3.3 mg (5%) of the desired acid as a colorless film. Calculated for C₂₄H₂₈ClNNaO₆S₂: m/z 548.0944. Found: 548.0940.

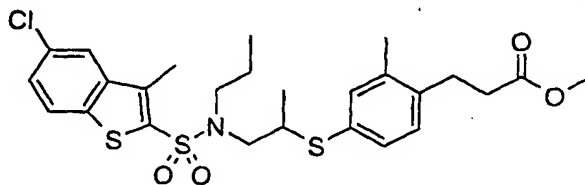
Example 205

3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenyl)-propionic acid



Step A

3-(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenyl)-propionic acid methyl ester



20

The compound of 4,4-dimethyl-2-(triphenyl-λ⁵-phosphanyl)-[1,2,5]thiadiazolidine 1,1-dioxide (190 mg, 0.46 mmol, 1.5 eq.) was added to a solution of 3-(4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid (69 mg, 0.33 mmol, 1.1 eq.) and 5-chloro-3-methyl-benzo[b] thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (109 mg,

25

-273-

0.30 mmol, 1 eq.) in anhydrous toluene (3 mL). The mixture was stirred for 17 h and rotary evaporated. The resultant material was eluted (100 mL 5% EtOAc/hex, 100 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex) through a chromatotron (1 mm plate) to yield about 21 mg (13%) of the methyl ester as a colorless oil.

5

Step B

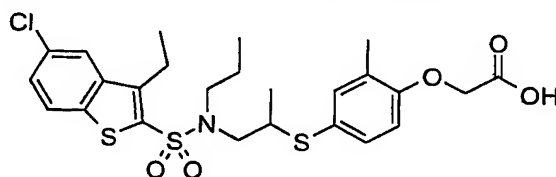
3-(4-{2-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenyl)-propionic acid

The compound of 3-(4-{2-[(5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenyl)-propionic acid methyl ester (21 mg, 3.8 mmol) was dissolved in EtOH (2 mL) and 5 M aq NaOH (0.2 mL). After stirring for 17 h, the mixture was rotary evaporated. The resultant residue was acidified with 1 M aq HCl (5 mL) and then extracted with CH₂Cl₂ (5 mL). The organic layer was dried (anhydrous MgSO₄) and rotary evaporated (50°C) yielding the crude acid as a colorless film. The material was divided into two samples. Each sample was chromatographed by reverse-phase (10 mL 0.1% TFA in 65% CH₃CN/H₂O, 10 mL CH₃CN) through 500-mg C₁₈ cartridges to yield about 11 mg (54%) of the purified acid. Calculated for C₂₅H₃₀ClNNaO₄S₃: m/z 562.0923. Found: 562.0914.

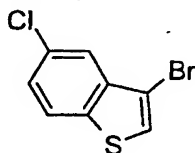
20

Example 206

(4-{2-[(5-Chloro-3-ethyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

3-Bromo-5-chloro-benzo[*b*]thiophene



25

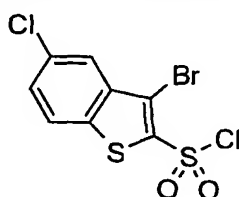
A solution of bromine (2.2 mL, 6.9 g, 43 mmol, 1.1 equiv) in AcOH (20 mL) was added to a solution 5-chloro-benzo[*b*]thiophene (6.65 g, 39.4 mmol,

-274-

1 equiv) in AcOH (20 mL), and the mixture was heated at 50°C for 1 h and the volatiles were removed by rotary evaporation (50°C). The resultant material was dissolved in CH₂Cl₂ (80 mL), washed with saturated aq. NaHCO₃ (80 mL), dried (anhydrous Na₂SO₄), and rotary evaporated (50°C) to give about 9.23 g (94.6%) of crude product as a light-brown solid.

Step B

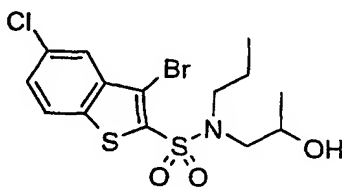
3-Bromo-5-chloro-benzo[*b*]thiophene-2-sulfonyl chloride



Chlorosulfonic acid (1.91 g, 3 equiv) was added to a solution of 3-bromo-5-chloro-benzo[*b*]thiophene (1 g, 0.004 mol, 1 equiv) in 1,2-dichloroethane (20 mL) at 0°C and warmed to room temperature, and then added to a mixture of EtOAc (100 mL) and saturated aq NaCl (100 mL). The organic layer was dried (anhydrous Na₂SO₄) and rotary evaporated giving 3.2 g of the crude material. The material was eluted (10-70% EtOAc/hex) on chromatotron to yield about 0.88 g of the title compound.

Step C

3-Bromo-5-chloro-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide



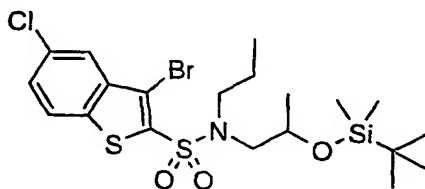
A solution of 3-bromo-5-chloro-benzo[*b*]thiophene-2-sulfonyl chloride (0.88 g, 2.5 mmol, 1 equiv) in anhydrous CH₂Cl₂ (10 mL) was added to a solution of 1-amino-2-propanol (0.24 mL, 0.23 g, 3.1 mmol, 1.2 equiv) and triethylamine (0.72 mL, 0.52 g, 5.2 mmol, 2.0 equiv) in anhydrous CH₂Cl₂ (15 mL) cooled to 0°C. The solution was washed with 1 M aq HCl (10 mL), dried (anhydrous Na₂SO₄), and rotary evaporated (50°C) to give about 0.80 g (82%) of the secondary amide as a light-yellow solid. The solid was dissolved in anhydrous DMF (15 mL) and cesium carbonate (1.1 g, 3.4 mmol, 1.3 equiv) was added followed by 1-iodopropane (0.32 mL, 0.56 g, 3.3 mmol, 1.3 equiv).

-275-

The reaction mixture was stirred at 50 °C. After 1 h, the mixture was poured into 1 M aq HCl (25 mL), and extracted with Et₂O (2 x 25 mL). The organic layer was dried (anhydrous Na₂SO₄) and rotary evaporated (50°C) to give about 0.85 g (78%) of tertiary amide as a yellow oil. The solid was eluted (200 mL 30% EtOAc/hex) through a chromatotron (2 mm plate) yielding about 0.62 g (57%) of the title compound as an off-white crystalline solid. Calculated for C₁₄H₁₈BrClNO₃S₂: m/z 425.9600. Found: 425.9618.

Step D

3-Bromo-5-chloro-benzo[*b*]thiophene-2-sulfonic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide

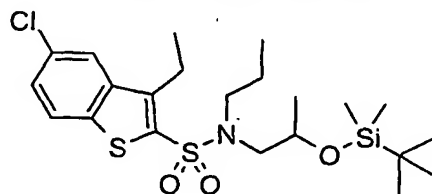


The compound of *tert*-butyldimethylsilyl chloride (0.39 g, 2.6 mmol, 2.0 equiv) was added to a solution of 3-bromo-5-chloro-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (0.55 g, 1.3 mmol, 1 equiv) and imidazole (0.18 g, 2.6 mmol, 2.1 equiv) in anhydrous CH₂Cl₂ (15 mL). After stirring for about 71 h, the mixture was rotary evaporated, which was then taken up in Et₂O (30 mL) and washed with saturated aq NH₄Cl (2 x 15 mL) and NaHCO₃ (15 mL). The organic layer was dried (anhydrous Na₂SO₄) and rotary evaporated (50°C) giving 0.73 g (100%) of the crude product as a yellow oil. The solid was eluted (100 mL hexanes, 300 mL 5% EtOAc/hex) through a chromatotron (4 mm plate) yielding about 0.59 g (85%) of the title compound as a yellow crystalline solid. Calculated for C₂₀H₃₂BrClNO₃S₂Si: m/z 540.0465. Found: 540.0430.

-276-

Step E

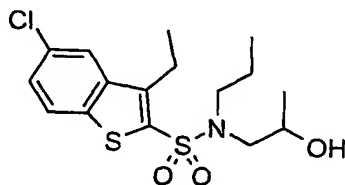
5-Chloro-3-ethyl-benzo[*b*]thiophene-2-sulfonic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide



5 Under argon, butyllithium (1.6 M in hexanes; 350 μ L, 0.56 mmol, 1.1 equiv) was added over a period of 2 min to a solution of 3-bromo-5-chloro-benzo[*b*]thiophene-2-sulfonic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide (277 mg, 0.512 mmol, 1 equiv) in anhydrous THF (15 mL) cooled to -78°C . After stirring for 60 min, iodoethane (filtered through alumina; 200 μ L, 390 mg, 2.5 mmol, 4.9 equiv) was added to the reaction solution and allow the reaction solution to warm slowly. After stirring for 2 h, the solution was quenched with saturated aq NaHCO_3 (10 mL). Et_2O (10 mL) was added and the organic layer was separated, dried (anhydrous MgSO_4), and rotary evaporated (50°C) to give about 239 mg of a brown oil. The material was purified by chromatography (50% $\text{CH}_2\text{Cl}_2/\text{hex}$) to yield about 94 mg (37%) of the desired compound as an oil. Calculated for $\text{C}_{22}\text{H}_{37}\text{ClINO}_3\text{S}_2\text{Si}$: m/z 490.1673. Found: 490.1666.

Step F

5-Chloro-3-ethyl-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide



20 About 5 M aq HCl (5 mL) was added to a solution of 5-chloro-3-ethyl-benzo[*b*]thiophene-2-sulfonic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide (94 mg) in EtOH (5 mL) and the mixture was stirred for 63 h. The mixture was rotary evaporated (75°C ; azeotroping with MeOH and then CH_2Cl_2) to yield about 75 mg of the title compound as an oil. Calculated for $\text{C}_{16}\text{H}_{22}\text{ClINNaO}_3\text{S}_2$: m/z 398.0627. Found: 398.0602.

-277-

Step G

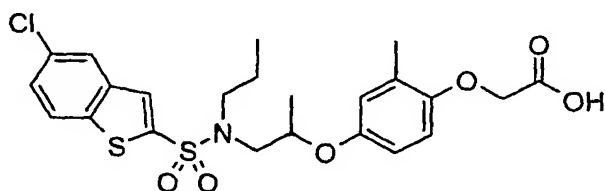
(4-{2-[(5-Chloro-3-ethyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

The compound of 4,4-dimethyl-2-(triphenyl- λ^5 -phosphanyl)-

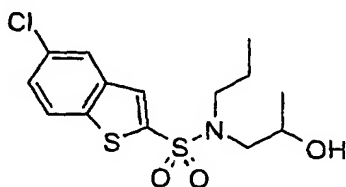
- 5 [1,2,5]thiadiazolidine 1,1-dioxide (120 mg, 0.29 mmol, 1.5 equiv) was added to a solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (48 mg, 0.21 mmol, 1.1 equiv) and 5-chloro-3-ethyl-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-
 10 amide (73 mg, 0.19 mmol, 1 equiv) in anhydrous toluene (3 mL). The mixture was stirred for 16 h and rotary evaporated. The resultant material was eluted (100 mL 5% EtOAc/hex, 200 mL 10% EtOAc/hex, 150 mL 20% EtOAc/hex) through a chromatotron (1 mm plate) yielding 6.1 mg (5.4%) of the ethyl ester as a colorless oil, which was dissolved in EtOH (1 mL) and 5 M aq NaOH (1 mL). After stirring for 40 min, the reaction solution was evaporated, and the resultant residue was acidified with 1 M aq HCl (5 mL) and then extracted with CH₂Cl₂ (2 x 5 mL). The organic layer was dried
 15 (anhydrous MgSO₄) and rotary evaporated (50°C) to yield about 4.8 mg (4.4%) of the product. Calculated for C₂₅H₃₀ClNO₅S₃: m/z 555.0975. Found: 555.0964.

Example 207

(4-{2-[(5-Chloro-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid

Step A

5-Chloro-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide



- 25 Under argon, butyllithium (1.6 M in hexanes; 1.3 mL, 2.1 mmol, 2.3 equiv) was added over a period of 2 min to a solution of 3-bromo-5-chloro-benzo[*b*]thiophene-2-

-278-

sulfonic acid (2-hydroxy-propyl)-propyl-amide (381 mg, 0.893 mmol, 1 equiv) in anhydrous THF (20 mL) cooled to -78°C . After stirring for 60 min, MeOH (200 μL ,) was added to quench the reaction solution. The solution (50°C) was evaporated, and the resultant residue was taken up in Et_2O (10 mL) and washed with saturated aq NH_4Cl (10 mL). The organic layer was separated, dried (anhydrous MgSO_4), and rotary evaporated (50°C) giving 297 mg (96%) of an orange-yellow oil. The oil was eluted (50 mL 1:1 CH_2Cl_2 /hex, 50 mL 1% EtOH in 1:1 CH_2Cl_2 /hex, 100 mL 2% EtOH in 1:1 CH_2Cl_2 /hex,) through a chromatotron (1 mm plate) to yield about 250 mg (80.5%) of the product as a light orange-red oil. Calculated for $\text{C}_{14}\text{H}_{19}\text{ClINO}_3\text{S}_2$: m/z 368.0495. Found: 368.0491.

Step B

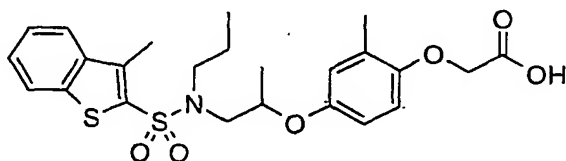
(4-{2-[(5-Chloro-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid

Diisopropyl azodicarboxylate (24 μL , 25 mg, 0.12 mmol, 1.0 equiv) was added over a period of 1 min to a solution of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (24 mg, 0.12 mmol, 1 equiv), 5-chloro-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (43 mg, 0.12 mmol, 1.0 equiv), and triphenylphosphine (32 mg, 0.12 mmol, 1.0 equiv) in anhydrous toluene (3 mL). The solution was stirred for 4.5 h and rotary evaporated. The resultant yellow oil was eluted (200 mL 5% EtOAc/hex, 200 mL 10% EtOAc/hex) through a chromatotron (1 mm plate) yielding 13 mg (20%) of the methyl ester as a colorless oil, which was dissolved in EtOH (2 mL) and 5 M aq NaOH (0.2 mL). After stirring for 62 h, solution was rotary evaporated, and the resultant residue was acidified with 1 M aq HCl (10 mL) and then extracted with CH_2Cl_2 (2 x 5 mL). The organic layer was dried (anhydrous MgSO_4) and rotary evaporated (50°C) to yield about 13 mg (21%) of the desired acid as a colorless film. Calculated for $\text{C}_{23}\text{H}_{26}\text{ClINO}_6\text{S}_2$: m/z 512.0968. Found: 512.0948.

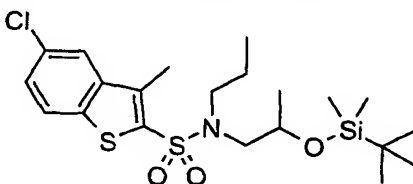
-279-

Example 208

(2-Methyl-4-{1-methyl-2-[(3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-phenoxy)-acetic acid

Step A

5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide

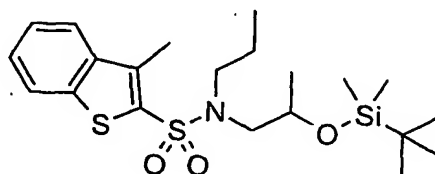


The compound of *tert*-butyldimethylsilyl chloride (318 mg, 2.11 mmol, 2.0 equiv) was added to a solution of 5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (382 mg, 1.06 mmol, 1 equiv) and imidazole (144 mg, 2.12 mmol, 2.1 equiv) in CH₂Cl₂ (10 mL). After stirring for 17 h, the mixture was evaporated and the resultant material was taken up in Et₂O (20 mL) and washed with saturated aq NH₄Cl (10 mL) and NaHCO₃ (10 mL). The organic layer was dried (anhydrous MgSO₄) and rotary evaporated giving 575 mg (114%) of the crude product as a colorless oil. The solid was eluted (100 mL hexanes, 150 mL 5% EtOAc/hex) through a chromatotron (2 mm plate) to yield about 478 mg (95.1%) of the purified material as a colorless crystalline solid. Calculated for C₂₁H₃₅ClNO₃S₂Si: *m/z* 476.1516. Found: 476.1508.

-280-

Step B

3-Methyl-benzo[*b*]thiophene-2-sulfonic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide

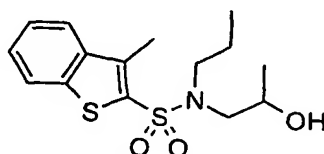


5 A mixture of 5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide (395 mg, 0.830 mmol), palladium on carbon (5% Pd; 49 mg), and triethylamine (2 mL) was shaken under 60 psig H₂ for 30 h. The mixture was filtered and the filtrate was rotary evaporated (50 °C) yielding 366 mg (100%) of the product as a colorless crystalline solid. Calculated for

10 C₂₁H₃₆NO₃S₂Si: m/z 442.1906. Found: 442.1895.

Step C

3-Methyl-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide



15 A solution of 3-methyl-benzo[*b*]thiophene-2-sulfonic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide (350 mg, 0.79 mmol) and trifluoroacetic acid (2 mL) in CH₂Cl₂ (10 mL) was stirred for 15 min. and the mixture was rotary evaporated. The resultant residue was chromatographed (100 mL hexanes, 100 mL 50% EtOAc/hex) through flash silica gel (35 mm x 35 mm dia.) to yield about 213 mg (82%) of the product as a yellow oil. Calculated for C₁₅H₂₂NO₃S₂: m/z 328.1041. Found: 328.1037.

-281-

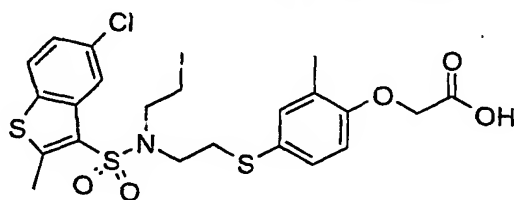
Step D

(2-Methyl-4-{1-methyl-2-[(3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl]-amino}-ethoxy)-phenoxy)-acetic acid

Diisopropyl azodicarboxylate (30 μ L, 31 mg, 0.15 mmol, 1.0 equiv) was added over a period of 1 min to a solution of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (30 mg, 0.15 mmol, 1.0 equiv), 3-methyl-benzo[*b*]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (50 mg, 0.15 mmol, 1 equiv), and triphenylphosphine (40 mg, 0.15 mmol, 1.0 equiv) in anhydrous toluene (3 mL). The solution was stirred for 17 h., and the mixture was rotary evaporated. The resultant yellow oil was eluted (200 mL 5% EtOAc/hex, 200 mL 10% EtOAc/hex) through a chromatotron (1 mm plate) yielding 20 mg (26%) of the methyl ester as a colorless oil. The oil was dissolved in EtOH (2 mL) and 5 M aq NaOH (0.2 mL) was added. After stirring for 2 h, the reaction solution was evaporated, and the resultant residue was acidified with 1 M aq HCl (10 mL) and then extracted with CH₂Cl₂ (2 x 5 mL). The organic layer was dried (anhydrous MgSO₄) and rotary evaporated (50°C) yielding 18 mg (24%) of the desired acid as a colorless film. Calculated for C₂₄H₂₉NO₆S₂: m/z 492.1515. Found: 492.1532.

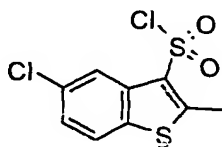
Example 209

20 (4-{2-[(5-Chloro-2-methyl-benzo[*b*]thiophene-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



Step A

5-Chloro-2-methyl-benzo[b]thiophene-3-sulfonyl chloride



25 Chlorosulfonic acid (72 μ L, 130 mg, 1.18 mmol, 3.0 equiv) was added to a solution of 5-chloro-2-methyl-benzo[*b*]thiophene (66 mg, 0.36 mmol, 1 equiv) in 1.2-

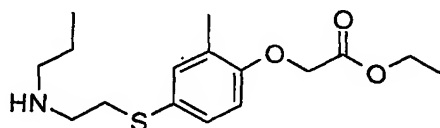
-282-

dichloroethane (1 mL) cooled to 0 °C. After stirring for an 1 h, the mixture was poured into a mixture of EtOAc (5 mL) and saturated aq NaCl (5 mL). The organic layer was separated, dried (anhydrous Na₂SO₄), and rotary evaporated (40°C) to yield about 82 mg (81%) of the product.

5

Step B

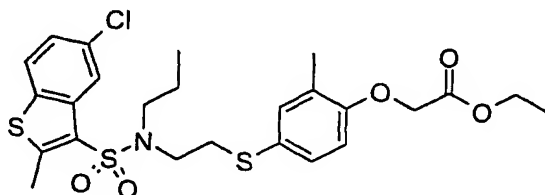
[2-Methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester



Trifluoroacetic acid (2.0 mL, 3.0 g, 26 mmol, 22 equiv) was added to a solution of {4-[2-(*tert*-butoxycarbonyl-propyl-amino)-ethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (490 mg, 1.19 mmol, 1 equiv) in CH₂Cl₂ (20 mL), the reaction solution was stirred for an 1 h. The solution (40°C) was evaporated to yield 713 mg (140%) of the trifluoroacetate salt as a colorless oil. The oil was dissolved in CH₂Cl₂ (50 mL) and saturated aq NaHCO₃ (20 mL) was added. The organic layer was separated, dried (anhydrous Na₂SO₄), and rotary evaporated (40°C) to yield about 349 mg (94.1%) of the free-base amine as a colorless oil. Calculated for C₁₆H₂₆NO₃S: m/z 312.1633. Found: 312.1652.

Step C

(4-{2-[(5-Chloro-2-methyl-benzo[*b*]thiophene-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



20

A solution of 5-chloro-2-methyl-benzo[*b*]thiophene-3-sulfonyl chloride (33 mg, 0.12 mmol, 1 equiv) in anhydrous CH₂Cl₂ (1 mL) was added to a solution of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (40 mg, 0.13 mmol, 1.1 equiv) and triethylamine (35 µL, 25 mg, 0.25 mmol, 2.1 equiv) in anhydrous CH₂Cl₂ (1 mL) cooled to 0°C. After stirring for an 1 h, the solution was diluted with CH₂Cl₂ (3 mL), washed with 0.2 M aq HCl (5 mL), dried (anhydrous

25

-283-

MgSO₄), and rotary evaporated (50°C) to give 72 mg (110%) of the sulfonamide as a yellow oil. The oil was eluted (50 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex) through a chromatotron (1 mm plate) to yield 44 mg (67%) of the purified material as a colorless film. Calculated for C₂₅H₃₁ClNO₅S₃: m/z 556.1053. Found: 556.1072.

5

Step D

(4-{2-[(5-Chloro-2-methyl-benzo[b]thiophene-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

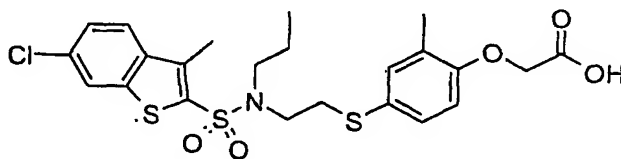
The compound of (4-{2-[(5-chloro-2-methyl-benzo[b]thiophene-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (43 mg, 0.077 mmol, 1 equiv) was dissolved in EtOH (4 mL) and 5 M aq NaOH (0.4 mL) was added. After stirring for 2 h, the reaction solution was rotary evaporated. The resultant residue was acidified with 1 M aq HCl (10 mL) and then extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (anhydrous MgSO₄) and rotary evaporated (50°C) to yield about 38 mg (93%) of the acid as a yellow film. Calculated for C₂₃H₂₇ClNO₅S₃: m/z 528.0740. Found: 528.0746.

10

15

Example 210

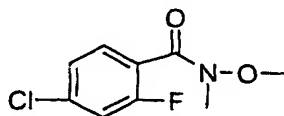
(4-{2-[(6-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



20

Step A

4-Chloro-2-fluoro-N-methoxy-N-methyl benzamide



2-Fluoro-4-chloro benzoic acid (2.00g, 11.5 mmol) was added to SOCl₂ (25 mL) and the mixture was heated at reflux for an hour. The excess SOCl₂ was removed on the rotary evaporator and the resulting oil was dissolved in CH₂Cl₂ (20mL) and added to a stirred mixture of N-methylN-methoxy hydroxylamine hydrochloride

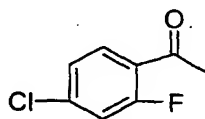
25

-284-

(1.25 g, 12.8 mmol) and pyridine (2.50 mL, 30 mmol) in CH_2Cl_2 (50 mL) at 0°C under N_2 . The mixture was stirred overnight, diluted with fresh CH_2Cl_2 (100mL) and extracted with H_2O (3X 100 mL), 1N HCl (100 mL) and saturated NaHCO_3 (100mL), and then washed with brine and dried (MgSO_4). The mixture was filtered and evaporated to give about 2.06g(82%) of the title compound as a pale yellow liquid. NMR (CDCl_3) δ 7.4 (m, 1H), 7.2 (m, 1H), 7.15 (m, 1H), 3.5 (broad s, 3H), 2.4 (s, 3H).

Step B

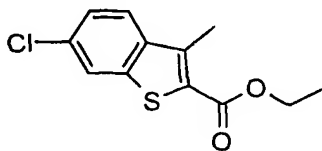
1-(4-Chloro-2-fluoro-phenyl) ethanone



CH_3Li (4.30 mL, 6.0 mmol) was added dropwise to a stirring solution of 4-chloro-2-fluoro-N-methoxy-N-methyl benzamide (1.09 g, 5.0 mmol) in THF (30mL) under N_2 at -70°C . The mixture was stirred for 1 hour at -70°C , and then at 0°C for 1 hour. The mixture was quenched with a saturated solution of NH_4Cl at 10°C and extracted with Et_2O (100 mL). The organic layer was dried (MgSO_4), filtered and evaporated to give a pale yellow liquid (0.84g), which was chromatographed on the chromatotron using a 4mm plate and then eluted with EtOAc-hexane (10:90) to afford about 0.52g (60%) of a pale yellow liquid. NMR CDCl_3 δ 7.9 (t, 1H), 7.25-1.5 (m, 2H), 2.6 (s, 3H).

Step C

6-Chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid ethyl ester



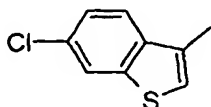
Cesium carbonate (4.5 g, 14 mmol, 2.0 equiv) was added to a solution of 1-(4-chloro-2-fluorophenyl)-ethanone (1.25 g, 7.24 mmol, 1.1 equiv) and ethyl 2-mercaptoacetate (0.75 mL, 0.82 g, 6.8 mmol, 1 equiv) in anhydrous DMF (15 mL). The mixture was stirred at 80°C for 1 h and then stirred at 20°C for 14 h. The mixture was poured into H_2O (75 mL) and extracted with Et_2O (2 x 50 mL). The combined organic

-285-

layers were dried (anhydr Na_2SO_4) and rotary evaporated (90 °C) to yield 1.43 g (82%) of product as a orange-yellow solid.

Step D

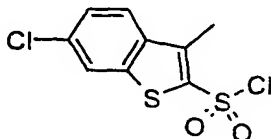
6-Chloro-3-methyl-benzo[*b*]thiophene



The compound of 6-chloro-3-methyl-benzo[*b*]thiophene-2-carboxylic acid ethyl ester (1.40 g, 5.50 mmol, 1 equiv) was dissolved in hot EtOH (30 mL) and 5 M NaOH (3 mL) was added. The solution was stirred for an hour and then rotary evaporated. The resultant solid was suspended in 0.2 M aq HCl (50 mL) and extracted with EtOAc (50 mL). The EtOAc layer was dried (anhydr Na_2SO_4) and rotary evaporated (50 °C) yielding 1.15 g (92.3%) of acid as a light yellow solid. The acid and copper powder (210 mg, 3.3 mmol, 0.60 equiv) was suspended in quinoline (60 mL), and the mixture was heated at 200 °C for 20 min and then allowed to cool. The mixture was diluted with Et₂O (300 mL) and filtered through Celite. The filtrate was washed with 5 M aq HCl (4 x 100 mL) to remove quinoline. The organic layer was dried (anhydrous Na_2SO_4) and rotary evaporated (50°C) to yield 1.62 g (161%) of crude product as a brown liquid. The liquid was eluted (200 mL hexanes) through a chromatotron (4 mm plate) to afford about 961 mg (95.7%) of the product as a colorless liquid.

Step E

6-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl chloride



Butyllithium (1.6 M in hexanes; 830 μL , 1.3 mmol, 1.2 equiv) was added to a solution of 6-chloro-3-methyl-benzo[*b*]thiophene (203 mg, 1.11 mmol, 1 equiv) in anhydrous THF (5 mL) cooled to -40°C in an acetonitrile/dry ice bath. The reaction solution was transferred to a regular ice bath (0 °C). After stirring for 30 min, the reaction solution was added to a solution of sulfonyl chloride (180 μL , 300 mg, 2.2 mmol, 2.0 equiv) in hexanes (2 mL) cooled to -40 °C. Then the solution was then transferred to a regular ice bath (0°C). After stirring for 30 min, the solution was quenched with

-286-

MeOH, and saturated aq NaHCO₃ was added to neutralize the acidic mixture. The organic layer was separated, dried (anhydrous MgSO₄), and rotary evaporated. The resultant brown oil was eluted (50 mL hexanes, 50 mL 10% EtOAc/hex) through a chromatotron (1 mm plate) to yield 51 mg (16%) of product as yellow-orange needles.

5

Step F

(4-{2-[(6-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

A solution of 6-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl chloride (47 mg, 0.17 mmol, 1 equiv) in anhydrous CH₂Cl₂ (1 mL) was added to a solution of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (57 mg, 0.18 mmol, 1.1 equiv) and triethylamine (47 µL, 34 mg, 0.34 mmol, 2.0 equiv) in anhydrous CH₂Cl₂ (1 mL) cooled to 0°C in an ice bath. After about 30 min, the solution was removed from the ice bath. After stirring for 2.5 h, the solution was diluted with CH₂Cl₂ (3 mL), washed with 0.2 M aq HCl (5 mL), dried (anhydrous MgSO₄), and rotary evaporated (50°C) to give 101 mg (110%) of the sulfonamide as a brown oil. The oil was eluted (50 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex) through a chromatotron (1 mm plate) to yield 55 mg (59%) of the purified sulfonamide ester as a colorless film, which was then dissolved in EtOH (5 mL) and 5 M aq NaOH (0.5 mL) was added. After stirring for 1 h, the solution was evaporated and the resultant residue was acidified with 1 M aq HCl (10 mL) and extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (anhydrous MgSO₄) and rotary evaporated (50°C) to yield about 52 mg (59%) of the acid as a yellow glass. Calculated for C₂₃H₂₇ClNO₅S₃: m/z 528.0740. Found: 528.0746.

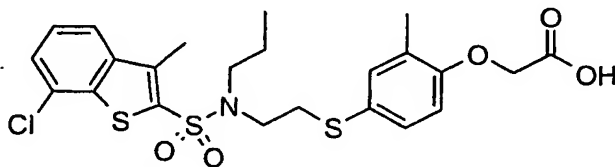
15

20

Example 211

(4-{2-[(7-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

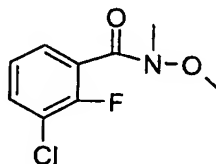
25



-287-

Step A

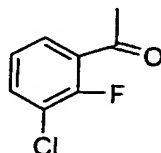
3-Chloro-2-fluoro-N-methoxy-N-methyl benzamide



The compound of 3-chloro-2-fluoro benzoyl chloride (3.50 g, 17.1 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirring solution of N-methoxy-N-methyl hydroxylamine hydrochloride (1.95 g, 20 mmol) and pyridine (3.60 mL, 44.5 mmol) in CH_2Cl_2 (80 mL) at 0°C . The mixture was stirred over the weekend and worked up as described in Example 210, Step A to give the title compound 3.56g (96%) as a colorless oil. MS (M/E): 218(m+1), 220(m+1).

Step B

1-(3-Chloro-2-fluoro-phenyl) ethanone

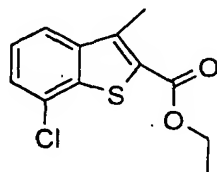


CH_3Li (12.00mL, 1.68 mmol) was added to a stirring solution of 3-chloro-2-fluoro-N-methoxy-N-methyl benzamide (3.26 g, 15.0 mmol) in THF (70 mL) under N_2 at -60°C . The mixture was stirred at -60°C for 3 h, and then warmed to -40°C and quenched with a saturated solution of NH_4Cl . The mixture was worked up as described in Example 210, Step B. Chromatography on the chromatron using a 4mm plate and eluting with EtOAc-hexane (5-95) affords about 1.20g(46%) of the title compound. NMR (CDCl_3) δ 7.68 (m, 1H), 7.45 (m, 1H), 7.18 (m, 1H), 7.65 (d, 3H).

-288-

Step C

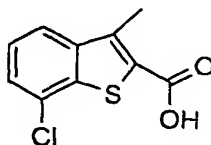
7-Chloro-3-methyl-benzo[b] thiophene-2-carboxylic acid ethyl ester



The compound of 1-(3-Chloro-2-fluoro-phenyl) ethanone (1.18 g, 6.8 mmol) was added to a stirring suspension of Cs_2CO_3 (4.17 g, 12.8 mmol) in dry DMF (20 mL) and then 2-mercapto ethyl acetate (0.77 g, 6.4 mmol) was added. The mixture was heated at 80°C for 1 hour. The mixture was stirred under N_2 overnight, and then poured into H_2O (100 mL) and extracted with Et_2O (150 mL). The Et_2O was extracted with H_2O (3x200mL), washed with brine, dried (MgSO_4) and filtered. A light brown solid was obtained upon evaporation. NMR (CDCl_3) δ 7.65 (d, 1 H), 7.45 (d, 1 H), 7.4 (t, 1 H), 4.40 (q, 2H), 2.68 (s, 3H), 1.44 (t, 3 H).

Step D

7-Chloro-3-methyl benzo [b] thiophene-2-carboxylic acid

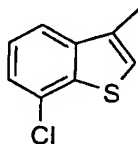


The compound of 7-Chloro-3-methyl-benzo [b] thiophene-2-carboxylic acid ethyl ester (1.10g, 4.3 mmol) was added to a stirring solution of 5M NaOH (30 mL) and EtOH (30 mL) under N_2 , and the mixture was heated at reflux for 30 minutes. The mixture was acidified to pH 4.0 with 37% HCl and extracted with Et_2O (300 mL). The Et_2O was washed with H_2O (2X 200mL) and brine, and then dried (MgSO_4), filtered and evaporated to give about 0.96g of a light brown solid. NMR ($\text{DMSO}-d_6$) δ 7.85 (d, 1H), 7.64 (d, 1H), 7.45 (t, 3 H).

-289-

Step E

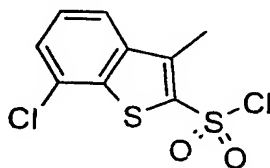
7-Chloro-3-methyl-benzo[b] thiophene



A solution of 7-chloro-3-methyl benzo [b] thiophene-2-carboxylic acid
5 (0.41g, 1.49 mmol) and Cu powder (0.069 g, 1.09 mmol) in quinoline (20 mL) was stirred
and heated at 200°C for 20 minutes. The mixture was cooled to ambient temperature and
diluted with Et₂O (100 mL), and then extracted with 2 M HCl (5x100 mL), washed with
brine, dried (MgSO₄) and filtered through celite. The filtrate was concentrated to a brown
oil and chromatographed on a 4mm plate eluting with EtOAc-hexane (5-95) to afford
10 about 0.19 g of oil. NMR (CDCl₃) δ7.62 (m, 1H), 7.35 (m, 2H), 7.05 (s, 1H), 2.42 (s,
3H).

Step F

7-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride



15 Butyllithium (1.6 M in hexanes; 1.8 mL, 2.9 mmol, 1.2 equiv) was added
to a solution of 7-chloro-3-methyl-benzo[b]thiophene (442 mg, 2.42 mmol, 1 equiv) in
anhydrous THF (5 mL) cooled in an acetonitrile/dry ice bath (-40°C). The solution was
transferred to an ice bath (0°C). After stirring for 20 min, the solution was added to a
solution of sulfonyl chloride (390 µL, 660 mg, 4.9 mmol, 2.0 equiv) in hexanes (5 mL)
20 cooled in an acetonitrile/dry ice bath (-40°C) (do not warm above -17°C during the
addition). Then the reaction solution was transferred to a regular ice bath (0°C). After
stirring for 1 h, saturated aq NaHCO₃ (5 mL) was added to quench the reaction. The
organic layer was separated, dried (anhydrous MgSO₄), and rotary evaporated (50°C) to
give 542 mg (79.7%) of crude product as a tan crystalline solid. The solid was eluted
25 (50 mL hexanes, 150 mL 10% EtOAc/hex) through a chromatotron (2 mm plate) to yield
187 mg (27.5%) of product as a light-yellow crystalline solid.

-290-

Step G

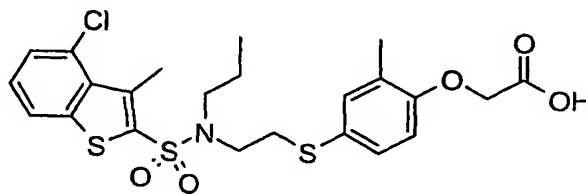
(4-{2-[(7-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

A solution of 7-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl chloride (54 mg, 0.19 mmol, 1 equiv) in anhydrous CH₂Cl₂ (1 mL) was added to a solution of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (66 mg, 0.21 mmol, 1.1 equiv) and triethylamine (54 µL, 39 mg, 0.39 mmol, 2.0 equiv) in anhydrous CH₂Cl₂ (1 mL) cooled in an ice bath (0°C). The solution was removed from the ice bath. After stirring for 2 h, the solution was diluted with CH₂Cl₂ (3 mL), washed with 0.2 M aq HCl (5 mL), dried (anhydrous MgSO₄), and rotary evaporated (50°C) to give 109 mg (100%) of the sulfonamide as a yellow oil. The oil was eluted (50 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex) through a chromatotron (1 mm plate) to yield 82 mg (77%) of the purified ester as a colorless film, which was then dissolved in EtOH (8 mL) and 5 M aq NaOH (0.8 mL) was added. After stirring for 3 h, the solution was concentrated, and the resultant residue was acidified with 1 M aq HCl (10 mL) and then extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (anhydrous MgSO₄) and rotary evaporated (50°C) to yield 65 mg (64%) of the acid as a white crystalline solid. Calculated for C₂₃H₂₇ClNO₅S₃: m/z 528.0740. Found: 528.0730.

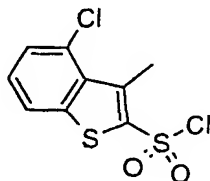
20

Example 212

(4-{2-[(4-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



-291-

Step A4-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl chloride

Butyllithium (1.6 M in hexanes; 4.2 mL, 6.7 mmol, 1.1 equiv) was added to a solution of 4-chloro-3-methyl-benzo[*b*]thiophene (1.10 g, 6.02 mmol, 1 equiv) in anhydrous THF (10 mL) cooled in an acetonitrile/dry ice bath (-40°C). The reaction solution was transferred to a regular ice bath (0°C). After stirring for 20 min, the reaction solution was added to a solution of sulfonyl chloride (1.5 mL, 2.5 g, 19 mmol, 3.1 equiv) in hexanes (10 mL) cooled in an acetonitrile/dry ice bath (-40°C) (do not warm above -3°C during the addition). The reaction solution was transferred to a regular ice bath (0°C). After stirring for 1 h, a saturated aq NaHCO₃ (10 mL) was added to quench the reaction. The organic layer was separated, dried (anhydrous Na₂SO₄), and rotary evaporated (40°C) to give 1.37 g (80.9%) of crude product as a tan crystalline solid. The material was eluted (150 mL hexanes, 150 mL 10% EtOAc/hex, 150 mL 20% EtOAc/hex) through a chromatotron (4 mm plate) to yield 746 mg (44.1%) of product as a cream-colored crystalline solid.

Step B(4-{2-[(4-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

A solution of 4-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl chloride (54 mg, 0.19 mmol, 1 equiv) in anhydrous CH₂Cl₂ (1 mL) was added to a solution of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (66 mg, 0.21 mmol, 1.1 equiv) and triethylamine (54 µL, 39 mg, 0.39 mmol, 2.0 equiv) in anhydrous CH₂Cl₂ (1 mL). After stirring for 13 h, the solution (50 °C) was concentrated to give a yellow film. The material was eluted (50 mL 10% EtOAc/hex, 50 mL 20% EtOAc/hex) through a chromatotron (1 mm plate) to yield 84 mg (79%) of the purified ester as a colorless film, which was then dissolved in EtOH (8 mL) and 5 M aq NaOH (0.8 mL) was added. After stirring for 1 h, the reaction solution was rotary evaporated, and the resultant residue was acidified with 1 M aq HCl (10 mL) and extracted with

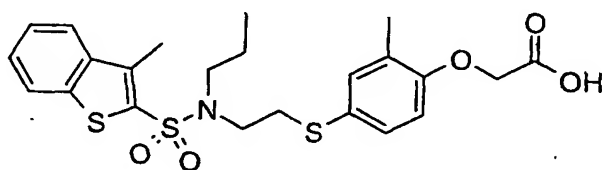
-292-

CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (anhydrous MgSO₄) and rotary evaporated (50°C) to yield about 83 mg (82%) of the acid as a light-yellow crystalline solid. Calculated for C₂₃H₂₇ClNO₅S₃: m/z 528.0740. Found: 528.0755.

5

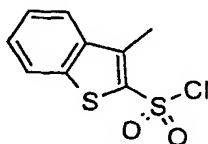
Example 213

(4-{2-[(3-Methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

10

3-Methyl-benzo[*b*]thiophene-2-sulfonyl chloride



Butyllithium (1.6 M in hexanes; 5.3 mL, 8.5 mmol, 1.1 equiv) was added to a solution of 3-methyl-benzo[*b*]thiophene (1.15 g, 7.76 mmol, 1 equiv) in anhydrous THF (10 mL) cooled in an acetonitrile/dry ice bath (-40°C). The reaction solution was transferred to a regular ice bath (0°C). After stirring for 20 min, the reaction solution was added over a period of 90 seconds to a solution of sulfuryl chloride (1.9 mL, 3.2 g, 24 mmol, 3.0 equiv) in anhydrous THF (10 mL) cooled in an acetonitrile/dry ice bath (-40°C) never warmed above -6 °C during the addition. The reaction solution was then transferred to a regular ice bath (0 °C). After stirring for 1 h, a saturated aq NaHCO₃ (10 mL) was slowly added to quench the reaction. The organic layer was separated, dried (anhydr Na₂SO₄), and rotary evaporated (50°C) to give 1.39 g (72.6%) of crude product as an orange-yellow crystalline solid. The material was eluted (150 mL hexanes, 100 mL 10% EtOAc/hex, 400 mL 20% EtOAc/hex) through a chromatotron (4 mm plate) to yield 737 mg (38.5%) of product as a yellow crystalline solid.

-293-

Step B

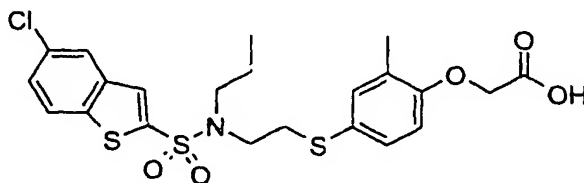
(4-{2-[(3-Methyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

A solution of 3-methyl-benzo[*b*]thiophene-2-sulfonyl chloride (50 mg, 0.20 mmol, 1 equiv) in anhydrous CH₂Cl₂ (1 mL) was added to a solution of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (70 mg, 0.22 mmol, 1.1 equiv) and triethylamine (56 µL, 41 mg, 0.40 mmol, 2.0 equiv) in anhydrous CH₂Cl₂ (1 mL). After stirring for 1.5 h, the solution was rotary evaporated to give a yellow film. The material was eluted (50 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex) through a chromatotron (1 mm plate) to yield 72 mg (68%) of the purified ester as a colorless film, which was then dissolve in EtOH (7 mL) and 5 M aq NaOH (0.7 mL) was added. After stirring for 16 h, the solution was concentrated, and the resultant residue was acidified with 1 M aq HCl (10 mL) and then extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (anhydrous MgSO₄) and rotary evaporated (50°C) to yield 65 mg (65.0%) of the acid as a colorless film.

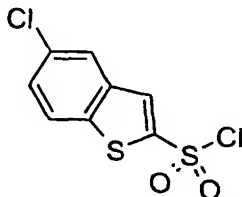
Calculated for C₂₃H₂₈NO₅S₃: m/z 494.1130. Found: 494.1134.

Example 214

(4-{2-[(5-Chloro-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



-294-

Step A5-Chloro-benzo[*b*]thiophene-2-sulfonyl chloride

Butyllithium (1.6 M in hexanes; 8.4 mL, 13 mmol, 1.1 equiv) was added to a solution of 5-chloro-benzo[*b*]thiophene (2.05 g, 12.2 mmol, 1 equiv) in anhydrous THF (20 mL) cooled in an acetonitrile/dry ice bath (-40°C). The reaction solution was transferred to a regular ice bath (0°C). After stirring for 15 min, the reaction solution was added over a period of 2 min to a solution of sulfonyl chloride (2.0 mL, 3.4 g, 25 mmol, 2.0 equiv) in hexanes (20 mL) cooled in an acetonitrile/dry ice bath (-40°C) never warming above -9°C during the addition. The reaction solution was transferred to a regular ice bath (0 °C). After stirring for 1 h, a saturated aq NaHCO₃ (20 mL) was added slowly to quench the reaction. The organic layer was separated, dried (anhydrous Na₂SO₄), and rotary evaporated (50°C) to give 2.72 g (83.8%) of crude product as a brown oil with brown crystals. The material was eluted (200 mL hexanes, 300 mL 10% EtOAc/hex) through a chromatotron (6 mm plate) to yield 1.37 g (42.2%) of product as a tan crystalline solid.

Step B(4-{2-[(5-Chloro-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methylphenoxy)-acetic acid

A solution of 5-chloro-benzo[*b*]thiophene-2-sulfonyl chloride (53 mg, 0.20 mmol, 1 equiv) in anhydrous CH₂Cl₂ (1 mL) was added to a solution of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester trifluoroacetate (94 mg, 0.22 mmol, 1.1 equiv) and triethylamine (83 µL, 60 mg, 0.60 mmol, 3.0 equiv) in anhydrous CH₂Cl₂ (1 mL). After stirring for 1.5 h, the reaction solution was concentrated to give a yellow film. The material was eluted (50 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex) through a chromatotron (1 mm plate) to yield 92 mg (86%) of the purified ester as a colorless film. The material was dissolved in EtOH (9 mL) and 5 M aq NaOH (0.9 mL) was added. After stirring for 63 h, the reaction solution rotary evaporated, and the resultant residue was acidified with 1 M aq HCl (10 mL) and then extracted with

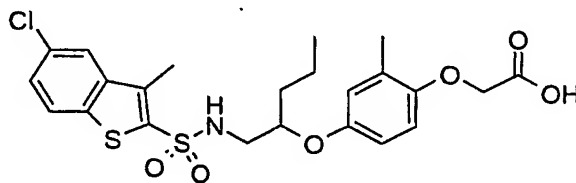
-295-

CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (anhydrous MgSO₄) and rotary evaporated (50°C) to yield 67 mg (66%) of the acid as an off-white crystalline solid. Calculated for C₂₂H₂₅ClNO₅S₃: m/z 514.0583. Found: 514.0583.

5

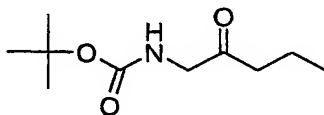
Example 215

(4-{1-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-methyl]-butoxy}-2-methyl-phenoxy)-acetic acid

Step A

10

(2-Oxo-pentyl)-carbamic acid tert-butyl ester



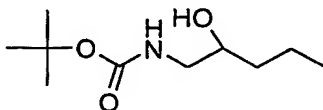
15

n-PrMgBr 2.0 M (12.5 mL, 25 mmol) was added to a stirring solution of n-(tert-butoxy carbonyl)glycine N-methoxy-N-methylamide (2.18 g, 10.7 mmol) in dry THF (30 mL) at -10 to 0°C. The resulting pale yellow solution was stirred at ambient temperature for 72 hours and then at reflux for 2.5 hours. The mixture was quenched at 0°C with a saturated solution of NH₄Cl. The Et₂O was added, and the organic layer was separated, washed with brine, dried (MgSO₄) and filtered. The filtrate was evaporated to give 1.93g of a pale yellow oil. NMR CDCl₃ δ 5.24 (b s, 1H), 4.00 (m, 2H), 2.40 (t, 2H), 1.65 (m, 2H), 1.25 (s, 9H), 0.90 (t, 3H).

20

Step B

(2-Hydroxy-pentyl)-carbamic acid tert butyl ester



25

NaBH₄ 0.380 g. 10 mmol) was added portion wise to a stirring solution of 2-oxo-pentyl)-carbamic acid tert-butyl ester (1.50 g, 7.45 mmol) in dry THF (50 mL) at ambient temperature. The resulting suspension was stirred overnight and quenched with

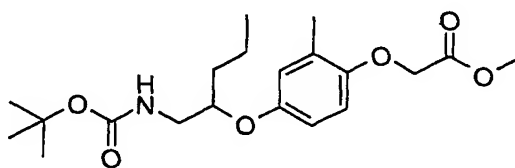
-296-

CH₃OH. The mixture was evaporated to a semisolid residue, which was partitioned between H₂O and CH₂Cl₂ (200 mL). The organic layer was separated, washed with brine, dried (MgSO₄) and filtered. The filtrate was evaporated to give 1.09g(72%) of a viscous liquid. MS(FAB⁺) 204.1.

5

Step C

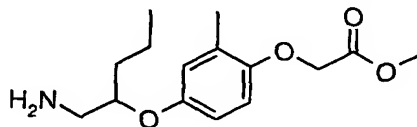
{4-[1-(*tert*-Butoxycarbonylamino-methyl)-butoxy]-2-methyl-phenoxy}-acetic acid methyl ester



Diisopropyl azodicarboxylate (0.64 mL, 0.66 g, 3.3 mmol, 1.0 equiv) was added over a period of 3 min to a solution of (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (633 mg, 3.23 mmol, 1 equiv), (2-hydroxy-pentyl)-carbamic acid *tert*-butyl ester (656 g, 3.23 mmol, 1.0 equiv), and triphenylphosphine (846 g, 3.23 mmol, 1.0 equiv) in anhydr toluene (60 mL). The solution was stirred for 14 h and the mixture was rotary evaporated. The resultant yellow oil was eluted (50 mL 5% EtOAc/hex, 100 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex, 300 mL 30% EtOAc/hex) through a chromatotron (6 mm plate) to yield 757 mg (61.5%) of product as nearly colorless oil. Calculated for C₂₀H₃₁NNaO₆: m/z 404.2049. Found: 404.2042.

Step D

[4-(1-Aminomethyl-butoxy)-2-methyl-phenoxy]-acetic acid methyl ester



20

Trifluoroacetic acid (2.9 mL, 4.3 g, 38 mmol, 20 equiv) was added to a solution of {4-[1-(*tert*-butoxycarbonylamino-methyl)-butoxy]-2-methyl-phenoxy}-acetic acid methyl ester (Example 210, Step C) (722 mg, 1.89 mmol, 1 equiv) in CH₂Cl₂ (20 mL). The colorless solution was stirred for 2 h. The reaction solution (50 °C) yielding 1.04 g (140%) of the trifluoroacetate salt was rotary evaporated as an orange oil. The oil was dissolved in CH₂Cl₂ (50 mL) and saturated aq NaHCO₃ (20 mL) was added. The organic layer was separated, dried (anhydrous Na₂SO₄), and rotary evaporated (40°C)

25

-297-

to yield 492 mg (92.4%) of the free-base amine as an orange oil. Calculated for $C_{15}H_{24}NO_4$: m/z 282.1705. Found: 282.1703.

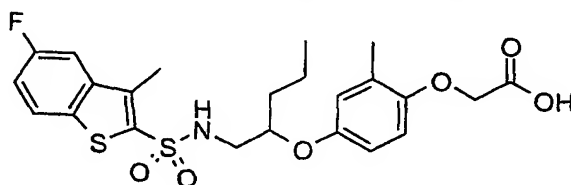
Step E

(4-{1-[(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonylamino)-methyl]-butoxy}-2-methyl-phenoxy)-acetic acid

A solution of 5-chloro-3-methylbenzo[*b*]thiophene-2-sulfonyl chloride (Oakwood; 237 mg, 0.843 mmol, 1 equiv) in anhydrous CH_2Cl_2 (4 mL) was added to a solution of [4-(1-aminomethyl-butoxy)-2-methyl-phenoxy]-acetic acid methyl ester (249 mg, 0.885 mmol, 1.05 equiv) and triethylamine (360 μ L, 260 mg, 2.6 mmol, 3.0 equiv) in anhydrous CH_2Cl_2 (4 mL). After 20 h, the reaction solution was rotary evaporated. The resultant material was eluted (50 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex, 150 mL 30% EtOAc/hex) through a chromatotron (2 mm plate) to yield 201 mg (45.3%) of the purified ester as a light-yellow film. The material was dissolved in EtOH (2 mL) and 5 M aq NaOH (0.2 mL) was added. After stirring for 16 h, the reaction solution was rotary evaporated, and the resultant residue was acidified with 1 M aq HCl (10 mL) and then extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried (anhydrous $MgSO_4$) and rotary evaporated (50°C) to yield about 188 mg (43.6%) of the acid as an off-white solid. Calculated for $C_{23}H_{27}ClNO_6S_2$: m/z 512.0968. Found: 512.0967.

Example 216

(4-{1-[(5-Fluoro-3-methyl-benzo[*b*]thiophene-2-sulfonylamino)-methyl]-butoxy}-2-methyl-phenoxy)-acetic acid



A suspension of 5-fluoro-3-methylbenzo[*b*]thiophene-2-sulfonyl chloride (211 mg, 0.797 mmol, 1 equiv) in anhydrous CH_2Cl_2 (4 mL) was added to a solution of [4-(1-aminomethyl-butoxy)-2-methyl-phenoxy]-acetic acid methyl ester (236 mg, 0.839 mmol, 1.05 equiv) and triethylamine (330 μ L, 240 mg, 2.4 mmol, 3.0 equiv) in anhydrous CH_2Cl_2 (4 mL). After stirring for 17 h, the reaction solution was rotary

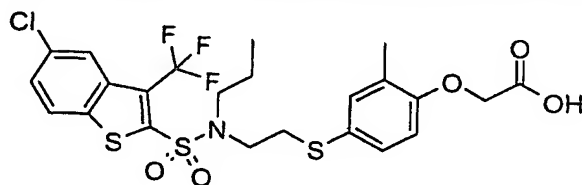
-298-

evaporated. The resultant material was eluted (50 mL 10% EtOAc/hex, 100 mL 20% EtOAc/hex) through a chromatotron (2 mm plate) to yield 117 mg (28.8%) of the purified ester as a colorless film. The material was dissolved in EtOH (2 mL) and 5 M aq NaOH (0.2 mL) was added. After stirring for 16 h, the reaction solution was rotary evaporated, and the resultant residue was acidified with 1 M aq HCl (10 mL) and then extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried (anhydrous MgSO₄) and rotary evaporated (50°C) to yield 105 mg (26.6%) of the acid as a white foam. Calculated for C₂₃H₂₇FNO₆S₂: m/z 496.1264. Found: 496.1264.

10

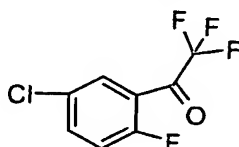
Example 217

(4-{2-[(5-Chloro-3-trifluoromethyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Step A

15

1-(5-Chloro-2-fluorophenyl)-2,2,2-trifluoro ethanone

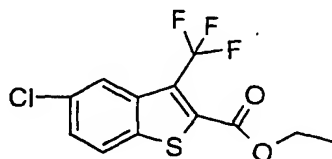


LDA 1.5 M (7.3 mL, 11.0 mmol) was added dropwise to a stirring solution of *p*-fluorochlorobenzene (1.30 g, 10 mmol) in anhydrous THF (15.0 mL) under N₂ at -70°C. The mixture was stirred at -70°C for 1 hour and then ethyl trifluoroacetate (1.56 g, 11 mmol) in THF (5.0 mL) was added dropwise. The resulting mixture was stirred at ambient temperature under N₂ overnight and quenched at 0°C with a saturated solution of NH₄Cl. The mixture was diluted with Et₂O, and the organic layer was separated, dried (MgSO₄), filtered, evaporated and chromatographed using a 4 mm plate and eluting with EtOAc-hexane (6:94) to give 0.98 g (43%) of a yellow liquid. NMR CDCl₃ δ 7.85 (m, 1H), 7.65 (m, 1H), 7.25 (m, 1H).

-299-

Step B

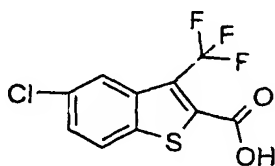
5-Chloro-3-trifluoromethyl-benzo [b] thiophene-2-carboxylic acid ethyl ester



A solution of 1-(5-Chloro-2-fluorophenyl)-2,2,2-trifluoro ethanone 0.95 g, 4.20 mmol) in CH₃CN (4.0 mL) was added to a stirring solution ethylthioacetate (0.51 mL, 4.60 mmol) and Et₃N (0.77 mL, 5.50 mmol) in CH₃CN (20 mL) at ambient temperature. The resulting yellow solution was heated at 80° C for 18 hours. After cooling to ambient temperature, the solvent was evaporated and the mixture was partitioned between Et₂O (100 mL) and 1 M NaOH (50 mL). The organic layer was separated, dried (MgSO₄) and filtered. The filtrate was evaporated, chromatographed on the chromatron using a 4mm plate and eluted with EtOAc-hexane (10:90) to give the ester as a white crystalline solid, 0.80 g (62%). NMR CDCl₃ δ 8.05 (s, 1H), 8.80 (d, 1H), 7.45 (d, 1H), 4.42 (q, 2H), 1.42 (t, 3H).

Step C

15 5-Chloro-3-trifluoromethyl-benzo [b] thiophene-2-carboxylic acid

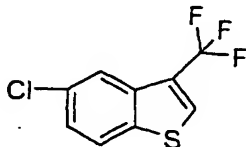


2 M NaOH (40 mL) was added to a stirring solution of 5-Chloro-3-trifluoromethyl-benzo [b] thiophene-2-carboxylic acid ethyl ester (1.75g, 5.7 mmol) in EtOH (40 mL), and the mixture was heated under reflux for 2 hours. EtOH was evaporated on the rotary evaporator and the resulting suspension was diluted with H₂O (100mL), acidified to pH 1 with 37% HCl. The resulting precipitate was extracted into EtOAc (250 mL), washed with brine, dried (MgSO₄), filtered and concentrated to give a white solid, 1.45g.

-300-

Step D

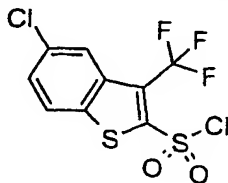
5-Chloro-3-trifluoromethylbenzo [b] thiophene



Copper powder (0.200g, 3.15 mmol) was added to a stirring solution of 5-chloro-3-trifluoromethyl-benzo [b] thiophene-2-carboxylic acid (1.45g, 5.18 mmol) in quinoline (14.0 mL), and the mixture was heat under N₂ at 200°C for 20 minutes. The mixture was diluted with Et₂O (20 mL) and filtered through celite. The filtrate was extracted with 1M HCl (3x 100 mL), washed with brine, dried (MgSO₄), filtered and evaporated to a brown liquid. The liquid was chromatographed on the chromatron on a 4mm plate eluting with hexane to give the title compound 1.10g as a clear liquid. Calculated for C₉H₄F₃SCl:235.9674; Found 235.9659.

Step E

5-Chloro-3-trifluoromethyl-benzo[b]thiophene-2-sulfonyl chloride



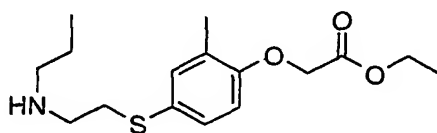
Butyllithium (1.6 M in hexanes; 3.2 mL, 5.1 mmol, 1.1 equiv) was added to a solution of 5-chloro-3-trifluoromethyl-benzo[b]thiophene (1.09 g, 4.61 mmol, 1 equiv) in anhydrous THF (20 mL) cooled in an acetonitrile/dry ice bath (-40°C). The reaction solution was transferred to a regular ice bath (0 °C). After stirring for 10 min, the reaction solution was added over a period of 1 min to a solution of sulfuryl chloride (750 µL, 1.3 g, 9.3 mmol, 2.0 equiv) in anhydrous THF (20 mL) in an acetonitrile/dry ice bath (-40°C) never warming above -8°C during the addition. The reaction solution was transferred to a regular ice bath (0°C). After stirring for 1 h, a saturated aq NaHCO₃ (20 mL) was slowly added to quench the reaction. The organic layer was separated, dried (anhydrous Na₂SO₄), and rotary evaporated (50 °C) to give 1.23 g (79.7%) of a crude product as an orange-brown oil. The material was eluted (200 mL hexanes, 100 mL 5%

-301-

EtOAc/hex, 100 mL 10% EtOAc/hex) through a chromatotron (4 mm plate) to yield 355 mg (23.0%) of product as an off-white crystalline solid.

Step F

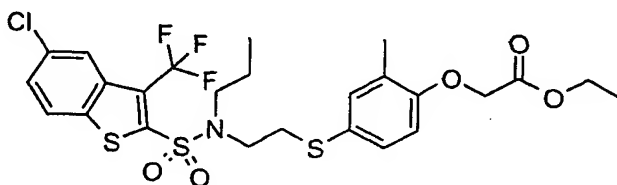
[2-Methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester



The compound of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester trifluoroacetate (545 mg, 1.28 mmol) was dissolved in CH₂Cl₂ (30 mL) and then saturated aq NaHCO₃ (20 mL) was added. The organic layer was separated, dried (anhydrous Na₂SO₄), and rotary evaporated (40 °C) to yield 235 mg (58.9%) of the free-base amine as a colorless oil.

Step G

(4-{2-[(5-Chloro-3-trifluoromethyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



The compound of 5-chloro-3-trifluoromethyl-benzo[*b*]thiophene-2-sulfonyl chloride (100 mg, 0.298 mmol, 1 equiv) was added to a solution of [2-methyl-4-(2-propylamino-ethylsulfanyl)-phenoxy]-acetic acid ethyl ester (100 mg, 0.321 mmol, 1.1 equiv) and triethylamine (85 µL, 62 mg, 0.61 mmol, 2.0 equiv) in anhydrous CH₂Cl₂ (2 mL). After stirring for 1 h, the reaction solution was transferred to a chromatotron (1 mm plate) and eluted (100 mL hexanes, 100 mL 10% EtOAc/hex, 50 mL 20% EtOAc/hex) to yield 133 mg (73.1%) of the purified ester as a colorless film.

Step H

(4-{2-[(5-Chloro-3-trifluoromethyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

The compound of (4-{2-[(5-chloro-3-trifluoromethyl-benzo[*b*]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (156 mg, 0.256 mmol) was dissolved in EtOH (16 mL) and 5 M aq NaOH (1.6 mL) was

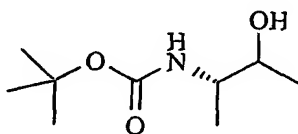
-302-

added. After stirring for 14 h, the reaction solution was rotary evaporated. The resultant residue was acidified with 1 M aq HCl (15 mL) and then extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried (anhydrous MgSO₄), rotary evaporated (40 °C), and placed under high vacuum (8 mtorr) for 4 hours to yield 104 mg (69.9%) of the acid as a white crystalline solid. Calculated for C₂₃H₂₄ClF₃NO₅S₃: m/z 582.0457. Found: 582.0443.

Elemental analysis for C₂₃H₂₃ClF₃NO₅S₃: calculated: C, 47.46; H, 3.98; N, 2.41; found: C, 47.57; H, 3.87; N, 2.29.

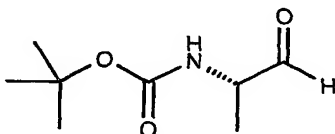
Example 218

(2-Hydroxy-1-methyl-propyl)-carbamic acid tert-butyl ester



Step A

(1-Methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester



A solution of [1-(methoxy-methyl)-carbamoyl]-ethyl]-carbamic acid tert-butyl ester (2g, 8.6mmol) in 20mL dry THF was cooled to -78°C. DIBAL (2eq, 8.6mL of 1M in toluene) was added and the reaction was stirred at -78°C for 30 minutes. The reaction was quenched with 10mL MeOH and 10mL water. The reaction was worked up in 50mL EtOAc and 50mL sat NaCl. The organics were dried with sodium sulfate and the organic layer was rotovaped to give 2.2g of the desired product. MS [E1+] 174 (M+H)⁺.

Step B

(2-Hydroxy-1-methyl-propyl)-carbamic acid tert-butyl ester

A solution of (1-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (2g, 11.5mmol) in 20mL dry THF was cooled to -78°C. MeLi (3eq, 24.6mL of 1.4M solution in ether) was added and the reaction was stirred at -78°C for 30 minutes. The reaction

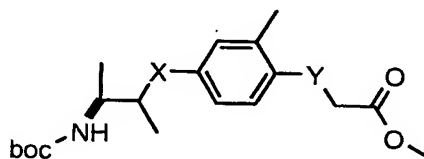
-303-

was allowed to slowly warm to RT. The mixture was added to 200mL EtOAc and washed with brine. The organics were dried with sodium sulfate and rotovaped to give 2.2 g of the desired alcohol. MS [EI+] 190 (M+H)⁺.

5

Example 219

Procedure A: General procedure used for Mitsunobu reactions



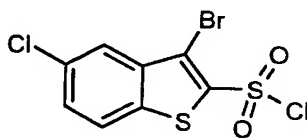
10

To a solution of primary or secondary alcohol in 25mL toluene was added phenol headpiece (1eq), DIAD (1 eq.), PPh₃ (1 eq.). The reaction was stirred overnight at RT. The reaction mixture was added to 100mL EtOAc. The organic layer was washed with brine and water (100mL each). The organics were dried with sodium sulfate and rotovaped to give crude material. The materials were separated on chromatotron (10-70% EtOAc/hex) to give desired product.

15

Example 220

3-Bromo-5-chloro-benzo[b]thiophene-2-sulfonyl chloride



20

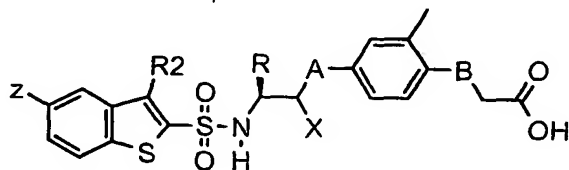
To a solution of 3-bromo-5-chloro-benzo[b]thiophene (1g, .004mol, 1eq) in 20mL of 1,2-dichloroethane at 0°C was added chlorosulfonic acid (3 eq., 1.91g). The solution was warmed to room temperature. The solution was added to 100mL EtOAc and 100mL brine for workup. The organic layer was dried with sodium sulfate and rotovaped to give 3.2 g of the crude material. The material was separated on the chromatatron (10-70% EtOAc/hex). The desired spot was rotovaped to give 0.88g of product. MS [EI+] 347 (M+H)⁺

25

-304-

Example 221

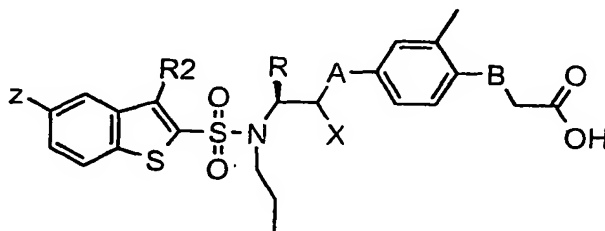
Procedure B: General procedure used for deprotection, sulfonyl chloride displacement, and hydrolysis



5 BOC-protected amines (Procedure A, Example 219) were added to a solution of trifluoroacetic acid (10mL). The reaction mixtures were stirred overnight at RT. The mixtures were added to 50mL EtOAc and washed with brine twice. The organic layers were dried with sodium sulfate and rotovaped. The materials were dissolved in 20mL DMF and sulfonyl chloride was added (1 eq.). The reaction mixture was stirred
10 overnight at RT. The reaction mixtures were each added to 50mL EtOAc and washed with brine twice. The organic layers were dried with sodium sulfate and rotovaped to give the desired esters. Some of these esters were held aside and used in Procedure C as described in Example 217. The materials were dissolved in EtOH (5mL) along with 5mL 5N NaOH. The reaction mixtures were stirred overnight at RT. The reaction mixtures
15 were added to 25mL EtOAc, and the solution was acidified with 10mL 5N HCl. The organic layer was dried with sodium sulfate and rotovaped to give the desired acid product. The compounds were characterized with MS.

Example 222

Procedure C: General procedure for N-alkylation and hydrolysis



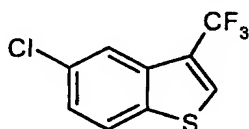
To a solution of ester (Procedure B, Example 221) in 20mL DMF at 0°C was added 3 eq. of propyl iodide along with 2 eq. of NaH (mineral oil). The mixtures were heated and stirred at 80°C overnight. The reaction mixtures were added to 50mL
25 EtOAc and washed with brine twice. The organic layers were dried with sodium sulfate

-305-

and rotovaped to give crude material. The material was separated on chromatotron (10-70% EtOAc/hex elution). The desired esters were isolated and identified with MS. The materials were dissolved in EtOH (5mL) along with 5mL 5N NaOH. The reactions were stirred overnight at RT. The mixtures were added to 25mL EtOAc and acidified with 10mL 5N HCl. The organic layer was dried with sodium sulfate and rotovaped to give the desired carboxylic acids. The compounds were characterized with MS.

Example 223

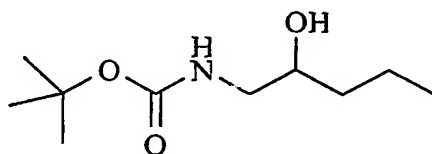
5-Chloro-3-trifluoromethyl-benzo[b]thiophene



To 3-bromo-5-chloro-benzo[b]thiophene (1g, .004mol, 1eq) was added copper powder (2.5eq, .010mmol, 0.64g) added along with 50mL DMSO. To this solution was slowly bubbled trifluoromethyl iodide. The reaction was stirred overnight at 120°C. The reaction mixture was filtered through celite. The filtrate was added to 100mL EtOAc for workup. The solution was washed with saturated NaCl twice. The organic layer was removed and dried with sodium sulfate. The solution was concentrated to give 500mg of crude material. The material was added to chromatotron and eluted with 10-70% EtOAc/hexanes. The product spot was identified with MS. About 200mg was isolated. MS [EI+] 237 (M+H)⁺.

Example 224

(2-Hydroxy-pentyl)-carbamic acid tert-butyl ester



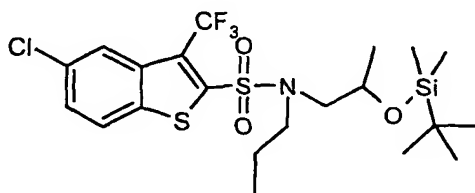
(2-Oxo-ethyl)-carbamic acid tert-butyl ester (2g, 12.5mmol) was dissolved in 20mL dry THF. The solution was cooled to -78°C. N-propyl magnesium bromide (3eq, 37.7mmol, 5.55g, 17.2mL of 30% solution in THF) was added, and the reaction was stirred at -78°C for 30 minutes. The reaction was quenched with 20mL

-306-

MeOH. The organics were removed and about 1.5g of product was identified by MS.
MS [EI+] 204 (M+H)⁺.

Example 225

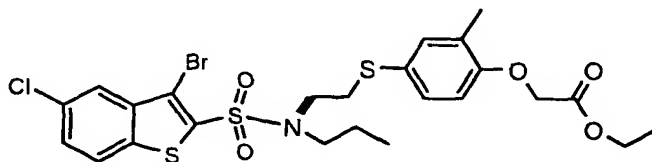
- 5 5-Chloro-3-trifluoromethyl-benzo[b]thiophene-2-sulfonic acid [2-(tert-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide



- The compound of 3-bromo-5-chloro-benzo[b]thiophene-2-sulfonic acid [2-(tert-butyl-dimethyl-silanyloxy)-propyl]-propyl-amide (0.100g, 0.18mmol, 1eq) was
10 added to a 3-necked flask. Copper powder (2.5eq, .46mmol, 0.030g) was added along with 50mL DMSO. To this solution was slowly bubbled trifluoromethyl iodide. The reaction was stirred overnight at 120°C. The reaction mixture was filtered through celite. The filtrate was added to 100mL EtOAc for workup and washed with saturated NaCl twice. The organic layer was removed and dried with sodium sulfate. The solution was
15 concentrated to give 500mg of crude material. The material was added to a chromatotron and eluted with 10-70% EtOAc/hexanes. About 32mg of product was isolated. MS [EI+] 530 (M+H)⁺.

Example 226

- 20 (4-{2-[(3-Bromo-5-chloro-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester



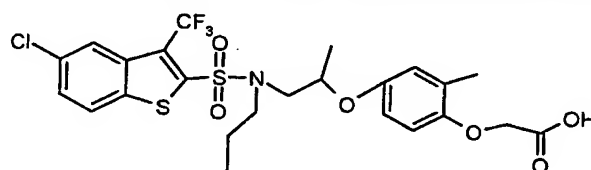
- {4-[2-(tert-Butoxycarbonyl-propyl-amino)-ethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (250mg, 0.6mmol) was dissolved in 5mL of
25 dichloromethane. Dimethyldiethylsilane (3eq, 1.8mmol, 160mg) was added along with 2mL TFA. The reaction was stirred at RT for 1 hr. The solvent was removed and

-307-

material dissolved in 5mL dichloromethane. Triethylamine (6eq, .5mL) was added along with 3-Bromo-5-chloro-benzo[b]thiophene-2-sulfonyl chloride (1eq, 210mg). The reaction mixture was filtered through celite. The filtrate was added to 100mL EtOAc for workup. The solution was washed with saturated NaCl twice. The organic layer was removed and dried with sodium sulfate. The solution was concentrated to give 500mg of crude material. The material was added to a chromatotron and eluted with 10-70% EtOAc/hexanes. About 102mg of material was isolated. MS [EI+] 622 (M+H)⁺.

Example 227

(4-{2-[(5-Chloro-3-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethoxy}-2-methyl-phenoxy)-acetic acid

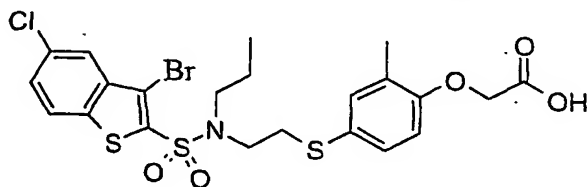


5-Chloro-3-trifluoromethyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (0.030g, 1eq, 0.07mmol) was added to 50mL toluene. (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (1eq, 0.07mmol), DIAD (0.014mL, 202.21amu, 1 eq.), PPh₃ (0.07mmol, .018g, 1 eq.) were added to the solution. The reaction was stirred overnight at RT. The mixture was added to 100mL EtOAc. The solution was washed with brine and water (100mL each). The organics were dried with sodium sulfate and rotovaped to give 35mg of crude material. The material was separated on a chromatotron (10-70% EtOAc/hex) to give 15mg of material. MS [EI+] 581 (M+H)⁺.

-308-

Example 228

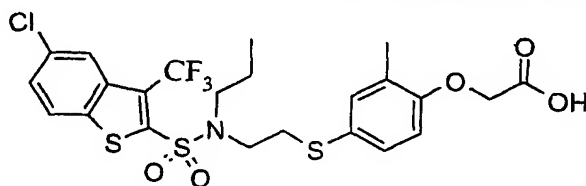
(4-{2-[(3-Bromo-5-chloro-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



5 The compound of (4-{2-[(3-bromo-5-chloro-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (10mg) was dissolved in 10mL EtOH. To the solution was added 10mL of 5N NaOH and the reaction was stirred overnight at RT. The solution was added to 100mL EtOAc and acidified with 20mL of 5N HCl. The organic layer was removed, dried with magnesium sulfate, and rotovaped to give 9.2g of material. MS [EI+] 594 (M+H)⁺.
10

Example 229

(4-{2-[(5-Chloro-3-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



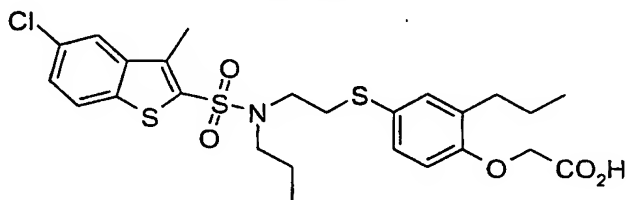
15 The compound of (4-{2-[(3-bromo-5-chloro-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (150mg, 0.24mmol, 1eq) was added to a 3-necked flask. Copper powder (2.5eq, 0.038g) was added along with 50mL DMSO. To this solution was slowly bubbled trifluoromethyl iodide. The mixture was stirred overnight at 120°C. and then filtered through celite. The filtrate was added to 100mL EtOAc for workup. The solution was washed with saturated NaCl twice. The organic layer was removed and dried with sodium sulfate. The solution was concentrated to give 100mg of crude material. The material was added to a chromatotron and eluted with 10-70% EtOAc/hexanes. About 15mg of material was
20 isolated. The material was dissolved in 10mL 5N HCl/10mL EtOH and stirred overnight
25

-309-

at RT. The solvent was removed and about 9.5mg of the title compound was isolated.
MS [EI+] 583 (M+H)⁺.

Example 230

- 5 (4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-
2-propyl-phenoxy)-acetic acid

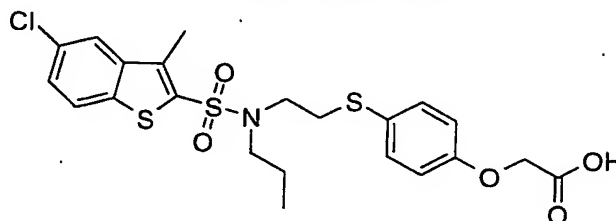


- A mixture of toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (200 mg, 0.40 mmol), (4-mercapto-2-propyl-phenoxy)-acetic acid ethyl ester (111 mg, 0.44 mmol) and Cs₂CO₃ (195 mg, 0.60 mmol) in 10 mL of dry DMF was heated to 45 °C for 2 h. The mixture was diluted with Et₂O and 1N HCl. The organic layer was washed with 1N HCl (3 x 10 mL) and brine and then dried over Na₂SO₄. Organic solvent was removed under the vacuum. Crude material was purified by chromatography (Hexanes/Acetone = 12/1) to provide
- 15 141 mg of (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-propyl-phenoxy)-acetic acid ethyl ester. The ethyl ester was then dissolved in 10 mL of THF/H₂O (1:1 by volume) with 0.8 mL of 1N aqueous LiOH. The mixture was allowed to stand at r.t. for 5 h. The mixture was diluted with Et₂O and 1N HCl. The organic layer was washed with 1N HCl (3 x 10 mL) and brine and then dried
- 20 over Na₂SO₄. The organic solvent was removed under the vacuum to give 133 mg of the title compound as white solid. ¹H NMR (400 MHz, CDCl₃); MS (ES⁺) *m/z* mass calculated for C₂₅H₃₀ClNO₅S₃ 555, found 556 (M + 1, 100%).

-310-

Example 231

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid

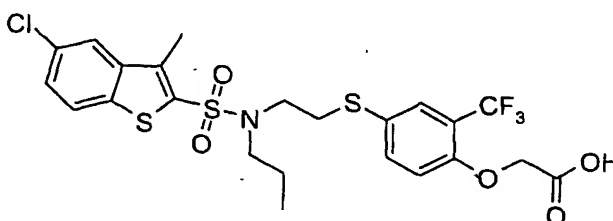


5 A mixture of toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (116 mg, 0.23 mmol), (4-Mercapto-phenoxy)-acetic acid ethyl ester (54 mg, 0.25 mmol) and Cs_2CO_3 (112 mg, 0.35 mmol) in 10 mL of dry DMF was heated to 45 °C for 2 h. The mixture was diluted with Et_2O and 1N HCl. The organic layer was washed with 1N HCl (3 x 10 mL) and brine and
10 then dried over Na_2SO_4 . The organic solvent was removed under the vacuum. Crude material was purified by chromatography (hexanes/acetone = 6/1) to provide 94 mg of (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid ethyl ester. The ethyl ester was then dissolved in 10 mL of THF/ H_2O (1:1 by volume) with 0.8 mL of 1N aqueous LiOH. The mixture was allowed
15 to stand at r.t. for 5 h. The mixture was diluted with Et_2O and 1N HCl. The organic layer was washed with 1N HCl (3 x 10 mL) and brine and then dried over Na_2SO_4 . The organic solvent was removed under the vacuum to give 89 mg of the title compound as white solid. ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{22}\text{H}_{24}\text{ClNO}_5\text{S}_3$ 513, found 514 ($M + 1$, 100%).

-311-

Example 232

(4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-trifluoromethyl-phenoxy)-acetic acid



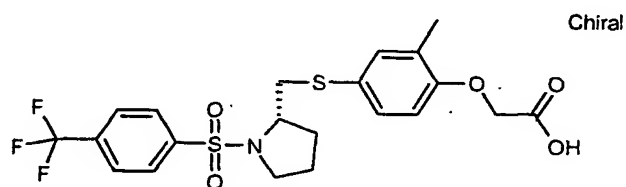
5 A mixture of toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (361 mg, 0.72 mmol), (4-Mercapto-2-trifluoromethyl-phenoxy)-acetic acid ethyl ester (200 mg, 0.72 mmol) and Cs_2CO_3 (468 mg, 1.44 mmol) in 15 mL of dry DMF was heated to 45 °C for 4 h. The mixture was diluted with Et_2O and 1N HCl. The organic layer was washed with 1N HCl
10 (3 x 10 mL), brine and dried over Na_2SO_4 . The organic solvent was removed under the vacuum. The crude material was purified by chromatography (hexanes/acetone = 7/1) to provide 355 mg of (4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-trifluoromethyl-phenoxy)-acetic acid ethyl ester. The ethyl ester was then dissolved in 10 mL of EtOH with 0.3 mL of 5N aqueous NaOH. The mixture
15 was allowed to stand at r.t. for 1 h. The mixture was diluted with Et_2O and 1N HCl. The organic layer was washed with 1N HCl (3 x 10 mL) and brine and then dried over Na_2SO_4 . The organic solvent was removed under the vacuum to give 388 mg of the title compound as white solid. ^1H NMR (400 MHz, CDCl_3); MS (ES^+) m/z mass calculated for $\text{C}_{23}\text{H}_{23}\text{ClF}_3\text{NO}_5\text{S}_3$ 581, found 582 ($\text{M} + 1$, 100%).

20

-312-

Example 233

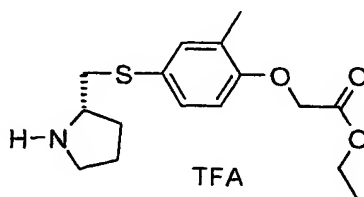
(S)-{2-Methyl-4-[1-(4-trifluoromethyl-benzenesulfonyl)-pyrrolidin-2-ylmethylsulfanyl]-phenoxy}-acetic acid



5

Step A

[2-Methyl-4-(pyrrolidin-2-ylmethylsulfanyl)-phenoxy]-acetic acid ethyl ester, TFA salt



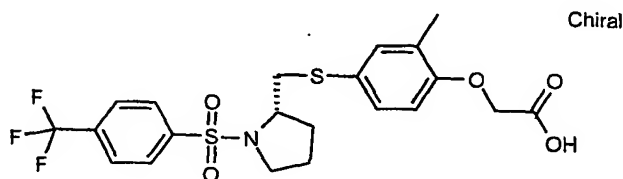
To a solution of (S)-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (2.4 g, 11.9 mmol) in toluene (50 mL) were added ADDP (4.6 g, 18.2 mmol) and n-Bu₃P (4.6 mL, 18.5 mmol) under nitrogen at 0~5 °C, followed by the addition of (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (2.6 g, 11.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was loaded on silica gel column and eluted with hexanes and ethyl acetate giving (s)-2-(4-ethoxycarbonylmethoxy-3-methyl-phenylsulfanylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (4.33 g, 88.7 %). The product was taken into methylene chloride (30 mL, treated with trifluoroacetic acid (5 mL) at 0~5 °C. and stirred for 2 h. Concentration of the mixture gives the title compound that was used for next step without further purification.

20

-313-

Step B

(S)-{2-Methyl-4-[1-(4-trifluoromethyl-benzenesulfonyl)-pyrrolidin-2-ylmethylsulfanyl]-phenoxy}-acetic acid



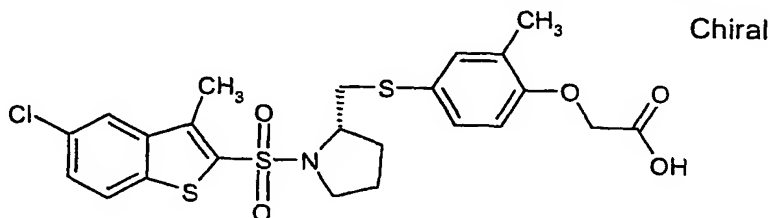
5 To a solution of [2-methyl-4-(pyrrolidin-2-ylmethylsulfanyl)-phenoxy]-acetic acid ethyl ester, TFA salt (210 mg, 0.5mmol) in methylene chloride (5 mL) was added triethyl amine (1 mL) and 4-trifluoromethyl-benzenesulfonyl chloride (122 mg, 0.5 mmol) at 0~5 °C. After stirred for 2h, the mixture was concentrated and the residue was treated with NaOH (5N, 1 mL) in ethanol (1 mL) for 2h. The mixture was concentrated and acidified with 5 N HCl (1 mL) and extracted with ethyl acetate. The extracts were dried and concentrated, and the crude product was purified by reversed phase HPLC (water-acetonitrile-0.1% TFA) giving the title compound. MS (ES): 490.2 ($M^+ + 1$).

The following Examples 234 to 239 were prepared by following the procedure as described in Example 233.

15

Example 234

(s)-{4-[1-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-pyrrolidin-2-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid

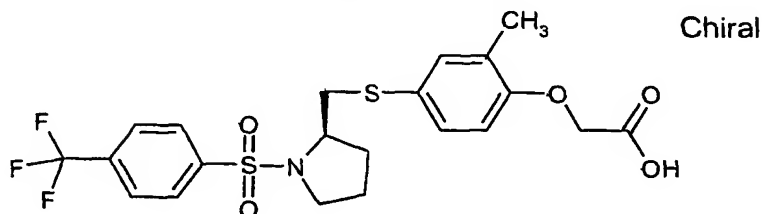


20 MS (ES): 528.2 (^{37}Cl , $M^+ + 1$), 526.2 (^{35}Cl , $M^+ + 1$).

-314-

Example 235

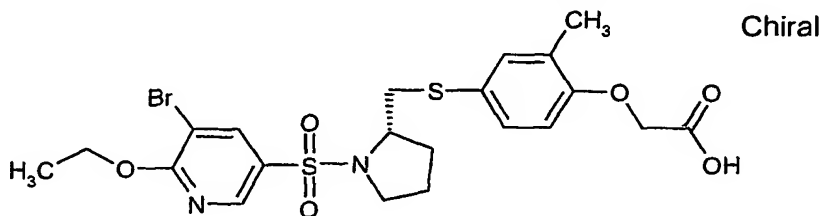
(R)-{2-Methyl-4-[1-(4-trifluoromethyl-benzenesulfonyl)-pyrrolidin-2-ylmethylsulfanyl]-phenoxy}-acetic acid



5 MS (ES): 490.0 ($M^+ + 1$).

Example 236

(s {4-[1-(5-Bromo-6-ethoxy-pyridine-3-sulfonyl)-pyrrolidin-2-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid

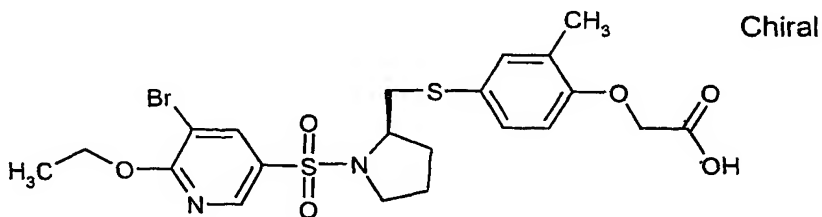


10

MS (ES): 545.4 (^{79}Br , $M^+ + 1$), 547.2 (^{81}Br , $M^+ + 1$).

Example 237

(R)-{4-[1-(5-Bromo-6-ethoxy-pyridine-3-sulfonyl)-pyrrolidin-2-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



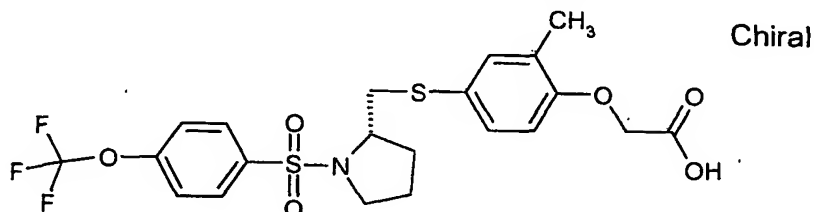
MS (ES): 545.4 (^{79}Br , $M^+ + 1$), 547.2 (^{81}Br , $M^+ + 1$).

20

-315-

Example 238

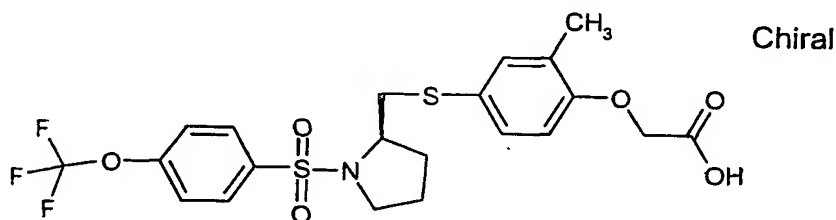
(S)-{2-Methyl-4-[1-(4-trifluoromethoxy-benzenesulfonyl)-pyrrolidin-2-ylmethylsulfanyl]-phenoxy}-acetic acid



5 MS (ES): 506.3 ($M^+ + 1$).

Example 239

(R)-{2-Methyl-4-[1-(4-trifluoromethoxy-benzenesulfonyl)-pyrrolidin-2-ylmethylsulfanyl]-phenoxy}-acetic acid



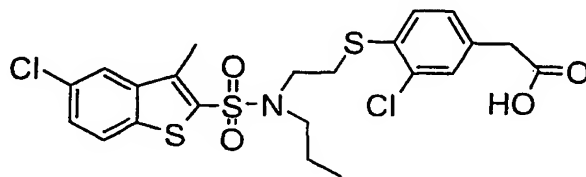
10

MS (ES): 506.3 ($M^+ + 1$).

Example 240

(3-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenyl)-acetic acid

15

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-ethyl)-propyl-amide

20 To a solution of 2-propylamino-ethanol (0.35 g, 3.44 mmol) in methylene chloride (34 mL) was added triethyl amine (7.2 mL) and 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (0.97 mg, 3.44 mmol) at 0~5 °C. After stirring for

-316-

2h, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (1.0 g).

Step B

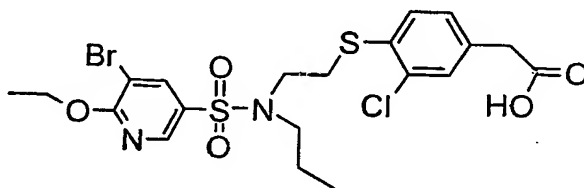
5 (3-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenyl)-acetic acid

To a solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-ethyl)-propyl-amide (180 mg, 0.5 mmol) in toluene (4 mL) were added ADDP (240 mg, 1 mmol) and n-Bu3P (0.24 mL, 1 mmol) under nitrogen at 0~5 °C. Then (3-chloro-4-mercapto-phenyl)-acetic acid (110 mg, 0.5 mmol) was added. The mixture was warmed to room temperature and stirred overnight. The mixture was loaded on silica gel column and eluted with hexanes and ethyl acetate giving (3-chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenyl)-acetic acid methyl ester (310 mg). The compound was then treated with NaOH (5N, 1 mL) in ethanol (1 mL) for 2h at 50 °C. The mixture was concentrated and acidified with 5 N HCl (1 mL) and extracted with ethyl acetate. The extracts were dried and concentrated, and the crude product was purified by reversed phase HPLC (water-acetonitrile-0.1% TFA) giving the title compound. MS (ES): 532.2(M⁺+1).

20 The following Examples 241 to 243 were prepared according to a procedure described in Example 240.

Example 241

(4-{2-[(5-Bromo-6-ethoxy-pyridine-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-3-chloro-phenyl)-acetic acid

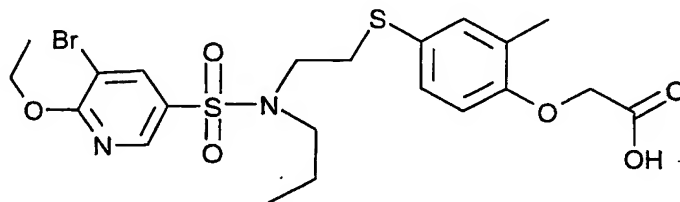


25 MS (ES): 551.2 (M⁺+1).

-317-

Example 242

(4-{2-[(5-Bromo-6-ethoxy-pyridine-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



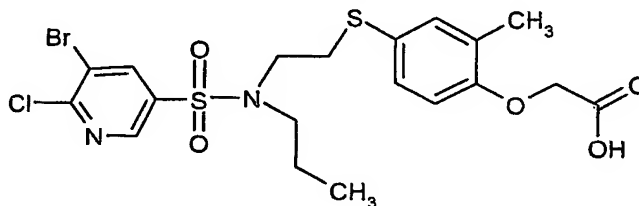
5

MS (ES): 547.3 ($M^+ + 1$).

Example 243

(4-{2-[(5-Bromo-6-chloro-pyridine-3-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

10

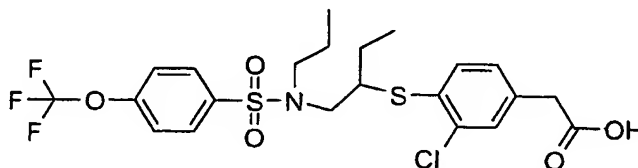


MS (ES): 537.1 ($M^+ + 1$).

15

Example 244

[3-Chloro-4-(1-{[propyl-(4-trifluoromethoxy-benzenesulfonyl)-amino]-methyl}-propylsulfanyl)-phenyl]-acetic acid



To a solution of (3-chloro-4-mercapto-phenyl)-acetic acid methyl ester (110 mg, 0.51 mmol) in DMF (3 mL) was added K_2CO_3 (104 mg, 0.75 mmol), followed by the addition of N-2-bromo-butyl)-N-propyl-4-trifluoromethoxy-benzenesulfonamide (217 mg, 0.5 mmol) in DMF (2 mL). After the mixture was stirred overnight, NaOH (5 N, 2 mL) and ethanol (1 mL) were added, and then heated at 60 °C for 2h. The mixture was concentrated, acidified by 5N HCl (2 mL), extracted with ethyl acetate, dried and

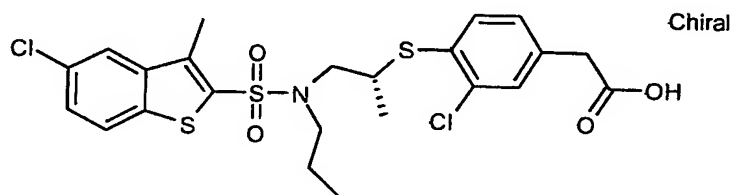
20

-318-

concentrated. Reversed phase HPLC purification (water-acetonitrile-0.1% TFA) afforded the title compound. MS (ES): 540.3 ($M^+ + 1$).

Example 245

5 (R)-(3-Chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-phenyl)-acetic acid



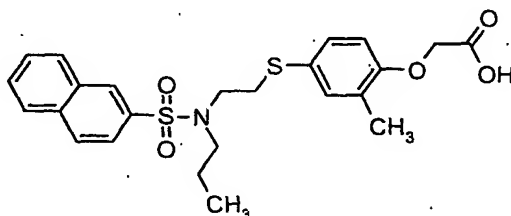
To a solution of (3-chloro-4-mercapto-phenyl)-acetic acid methyl ester (240 mg, 1.11 mmol) in DMF (6 mL) was added K_2CO_3 (240 mg, 1.7 mmol), followed by the addition of methanesulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethyl ester (442 mg, 1 mmol) in DMF (4 mL). After stirring at room temperature over a week, the mixture was diluted with ethyl acetate, washed with water, dried and concentrated. Column chromatography on silica gel afforded (R)-(3-chloro-4-{2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-1-methyl-ethylsulfanyl}-phenyl)-acetic acid methyl ester. This product was treated with NaOH (5 N, 1 mL) in ethanol (1 mL) at 60 °C for 2h. The mixture was then concentrated, acidified by 5N HCl (2 mL), extracted with ethyl acetate, dried and concentrated. Reversed phase HPLC purification (water-acetonitrile-0.1% TFA) gave the title compound (90 mg). MS (ES): 547.3 ($M^+ - 1$).

20 The following Examples 246 to 249 were prepared by following the procedure as described in Example 245.

-319-

Example 246

(2-Methyl-4-{2-[(naphthalene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-phenoxy)-acetic acid



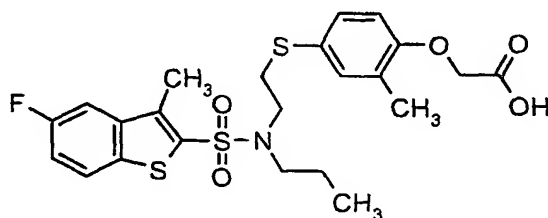
5

MS (ES): 472.1 ($M^+ - 1$).

Example 247

(4-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

10

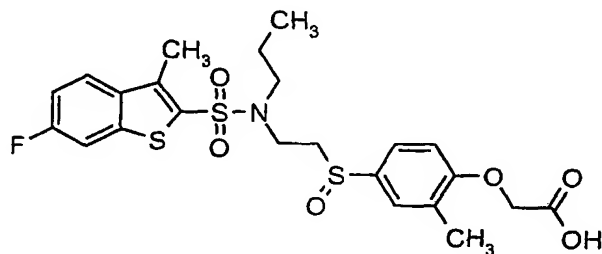


MS (ES): 510.1 ($M^+ - 1$).

Example 248

(4-{2-[(6-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethanesulfinyl}-2-methyl-phenoxy)-acetic acid

15



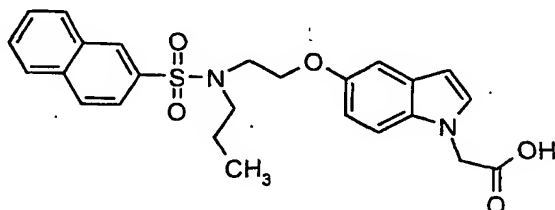
MS (ES): 526.06 ($M^+ - 1$).

20

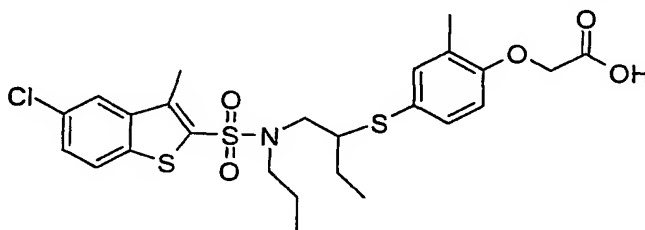
-320-

Example 249

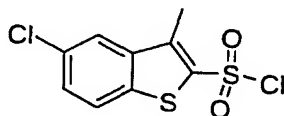
(5-{2-[(Naphthalene-2-sulfonyl)-propyl-amino]-ethoxy}-indol-1-yl)-acetic acid

MS (ES): 465.0(M⁺-1).Example 250

[4-(1-{[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid

Step A

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride

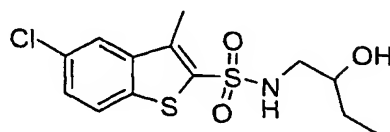


Chlorosulphonic acid (21.8 mL, 0.328mol) was added via syringe to 0 °C dichloroethane (118 mL). The compound of 5-chloro-3-methylbenzothiophene (20.0 g, 0.109mol) in dichloroethane (32 mL) was added dropwise to the solution. The resulting cranberry-colored solution thickened to a slurry and was stirred at room temperature. After 2h, the reaction slurry was poured over an ice/water bath. The resulting precipitate was washed with copious amounts of water and dried overnight in a vacuum oven to provide 26.0 g (84%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, 1H, *J* = 8.6 Hz), 7.75 (d, 1H, *J* = 2.0 Hz), 7.35 (dd, 1H, *J* = 8.6 Hz, 2.0 Hz), 2.45 (s, 3H). *R*_f = 0.53 in 33% acetone in hexanes.

-321-

Step B

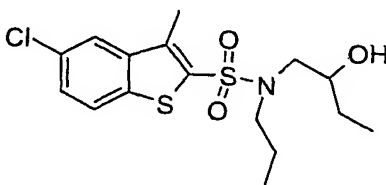
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-amide



- Dropwise, add 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (2.03 g, 7.22 mmol) in dichloromethane (20 mL) to a 0 °C solution of 1-amino-2-butanol (0.8 mL, 9.94 mmol) and triethylamine (2.0 mL, 14.4 mmol) in dichloromethane (80 mL). The resulting solution was stirred at ambient temperature for 1h, then diluted with dichloromethane and washed with water. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to provide a quantitative yield of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, 1H, *J* = 8.0 Hz), 7.45 (dd, 1H, *J* = 8.0 Hz, 1.8 Hz), 3.69-3.64 (m, 1H), 3.24 (dd, 1H, *J* = 13.3 Hz, 3.1 Hz), 3.92 (dd, 1H, *J* = 13.3 Hz, 8.0 Hz), 2.66 (s, 3H), 1.53-1.41 (m, 2H), 0.91 (t, 3H, *J* = 7.1 Hz). MS [EI+] 334 (M+H)⁺. R_f = 0.52 in 50% acetone in hexanes.

Step C

- 15 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-propyl-amide :



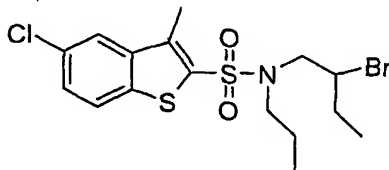
- A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-amide (2.41 g, 7.22 mmol) and 1-iodopropane (0.92 mL, 9.38 mmol) in dimethylformamide (120 mL) was treated with cesium carbonate (3.06 g, 9.38 mmol). The resulting mixture was heated to 50 °C under N₂ until all of the 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-amide was consumed. The reaction mixture was cooled to ambient temperature, and diluted with diethyl ether. The organic layer was washed with 1N HCl and water, dried over Na₂SO₄, and concentrated *in vacuo*. The crude material was purified by flash chromatography, using 20% acetone in hexanes as eluent, to provide 2.43 g (90%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, 1H, *J* = 2.3 Hz), 7.74 (d, 1H, *J* = 8.7 Hz), 7.46 (dd, 1H, *J* = 8.7 Hz, 2.3 Hz), 3.83-

-322-

3.76 (m, 1H), 3.35-3.16 (m, 4H), 2.69 (s, 3H), 2.33 (d, 1H, $J = 3.6$ Hz), 1.67-1.57 (m, 2H), 1.53-1.42 (m, 2H), 0.98 (t, 3H, $J = 7.3$ Hz), 0.82 (t, 3H, $J = 7.3$ Hz). MS [EI+] 376 (M+H)⁺. $R_f = 0.23$ in 20% acetone in hexanes.

Step D

5 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-butyl)-propyl-amide

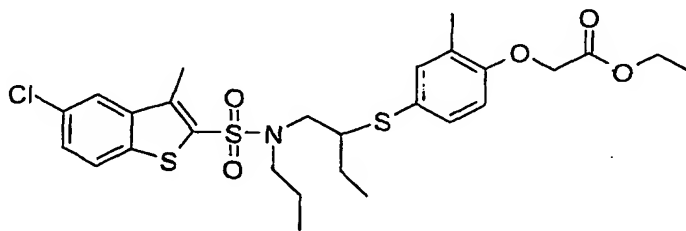


A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-butyl)-propyl-amide (3.34 g, 8.88 mmol) and carbon tetrabromide (4.42 g, 13.33 mmol) in dichloromethane (60 mL) was treated with triphenylphosphine (3.50 g, 13.33 mmol).

10 The resulting mixture was stirred at ambient temperature overnight, and then concentrated *in vacuo*. The residue was diluted with diethyl ether and filtered. The filtrate was adsorbed onto silica gel and purified by flash chromatography, using 10% acetone in hexanes as eluent, to provide 2.34 g (60%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, 1H, $J = 1.9$ Hz), 7.74 (d, 1H, $J = 8.6$ Hz), 7.45 (d, 1H, $J = 8.6$ Hz, 1.9 Hz), 4.17-4.10 (m, 1H), 3.73, 3.47 (AB_q, 1H, $J = 7.2$ Hz), 3.69, 3.51 (AB_q, 1H, $J = 7.2$ Hz), 3.37-3.30 (m, 1H), 3.23-3.15 (m, 1H), 2.68 (s, 3H), 2.13-2.08 (m, 1H), 1.78-1.51 (m, 3H), 1.08 (t, 3H, $J = 7.2$ Hz), 0.87 (t, 3H, $J = 7.2$ Hz).

Step E

20 [4-(1-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester



A 0 °C suspension of sodium hydride (0.17 g, 4.29 mmol) and (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (0.97g, 4.29mmol) in dry DMF (26mL) was treated with a solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-bromo-butyl)-propyl-amide (1.31g, 2.98mmol) in DMF (6mL). The resulting solution was

-323-

stirred at ambient temperature for 5h, and then quenched with 1N HCl (49mL). The reaction mixture was diluted with diethyl ether and washed with water. The organic layer was dried over sodium sulphate and adsorbed onto silica gel. The crude material was purified by flash chromatography, using 14% ethyl acetate in hexanes, to obtain 0.68g (39%) of the title compound. $R_f = 0.18$ in 20% acetone in hexanes. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, 1H, $J = 2.2$ Hz), 7.73 (d, 1H, $J = 8.6$ Hz), 7.44 (dd, 1H, $J = 8.6$ Hz, 2.2 Hz), 7.22 (d, 1H, $J = 1.4$ Hz), 7.18 (dd, 1H, $J = 8.6$ Hz, 2.9 Hz), 6.59 (d, 1H, $J = 8.6$ Hz), 4.62 (s, 2H), 4.26 (q, 2H, $J = 7.2$ Hz), 3.38 (dd, 1H, $J = 14.4$ Hz, 9.4 Hz), 3.24 (dd, 1H, $J = 14.4$ Hz, 5.8 Hz), 3.20-3.06 (m, 3H), 2.56 (s, 3H), 2.24 (s, 3H), 1.97-1.87 (m, 1H), 1.52-1.35 (m, 3H), 1.29 (t, 3H, $J = 7.2$ Hz), 1.29 (t, 3H, $J = 7.2$ Hz), 1.09 (t, 3H, $J = 7.2$ Hz), 0.81 (t, 3H, $J = 7.2$ Hz).

Step F

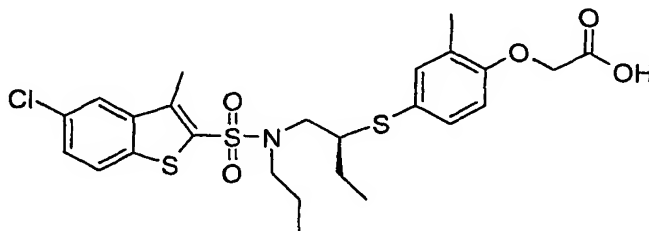
[4-(1-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl)-propylsulfanyl)-2-methyl-phenoxy]-acetic acid

A solution of [4-(1-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl)-propylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (0.68 g, 1.16 mmol) and 5N NaOH (0.7 mL) in a solution of dioxane (1 mL) and ethanol (8mL) was stirred at ambient temperature under nitrogen for 2h, and then concentrated *in vacuo*. The residue was diluted with 1N HCl, extracted with CH_2Cl_2 , dried over Na_2SO_4 , and concentrated *in vacuo* to provide 0.60 g (93%) of the title compound. ^1H NMR (400 MHz, CDCl_3) δ 7.74 (s, 1H), 7.71 (d, 1H, $J = 8.8$ Hz, 1.5 Hz), 7.42 (d, 1H, $J = 8.8$ Hz), 7.22 (s, 1H), 7.19 (d, 1H, $J = 8.8$ Hz), 6.61 (d, 1H, $J = 8.8$ Hz), 5.29 (d, 1H, $J = 2.2$ Hz), 4.68 (s, 2H), 3.39 (dd, 1H, $J = 13.9$ Hz, 8.8 Hz), 3.25 (dd, 1H, $J = 15.4$ Hz, 4.4 Hz), 3.20-3.07 (m, 3H), 2.57 (s, 3H), 2.22 (s, 3H), 1.96-1.86 (m, 1H), 1.53-1.35 (m, 3H), 1.09 (t, 3H, $J = 7.3$ Hz), 0.81 (t, 3H, $J = 7.3$ Hz). MS (ES^-) m/z mass calculated for $\text{C}_{25}\text{H}_{30}\text{O}_5\text{NS}_3\text{Cl}$ 555, found 554 (M-1) and 556 (M+1).

-324-

Example 251

[4-(1-{{(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid



5 The compound of [4-(1-{{(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-methyl}}-propylsulfanyl)-2-methyl-phenoxy]-acetic acid was resolved using chiral HPLC (ChiralPak AD 4.6 x 250mm, 90/10 heptane/3A EtOH, 1ml/min, 240 nm UV setting) to give enantiomers of isomer 1 (0.301 g, isomer 1, 100% ee) and isomer 2 (0.297 g, isomer 2, 97.5% ee). ¹H NMR (400 MHz, CDCl₃) δ 7.74 (s, 1H), 7.71 (d, 1H, *J* = 8.8 Hz, 1.5 Hz), 7.42 (d, 1H, *J* = 8.8 Hz), 7.22 (s, 1H), 7.19 (d, 1H, *J* = 8.8 Hz), 6.61 (d, 1H, *J* = 8.8 Hz), 5.29 (d, 1H, *J* = 2.2 Hz), 4.68 (s, 2H), 3.39 (dd, 1H, *J* = 13.9 Hz, 8.8 Hz), 3.25 (dd, 1H, *J* = 15.4 Hz, 4.4 Hz), 3.20-3.07 (m, 3H), 2.57 (s, 3H), 2.22 (s, 3H), 1.96-1.86 (m, 1H), 1.53-1.35 (m, 3H), 1.09 (t, 3H, *J* = 7.3 Hz), 0.81 (t, 3H, *J* = 7.3 Hz).

15

Example 252

No example with Example number 252.

20 Standard synthesis procedures were used in preparing many of the exemplified compounds or intermediates of the present invention. These standard procedures are described below:

Example 253

25 Standard Procedure (A): A mixture of 0.35 mmol sulfonyl chloride, 0.3 mmol 2-methyl-2-[4-(3-propylamino-propyl)-phenoxy]-propionic acid ethyl ester in 1mL CH₂Cl₂ and 200 μL triethylamine were placed in a 1 dram screw cap vial. The mixture was shaken for 18 h at an ambient temperature. The solvent was removed from the vial by evaporation, and the residue was dissolved in 1 mL ethanol and then 250 μL 5N NaOH

-325-

was added. The mixture was heated at 50°C for 1 h, which was then cooled and acidified with 350 μ L 5N HCl. The crude reaction was poured onto a Varian ChemElut 1003 cartridge and eluted with 10 mL CH_2Cl_2 . After evaporation, the crude compound was purified using mass-guided reverse phase HPLC.

5

Example 254

Standard Procedure (B): A solution of 0.265 mmol sulfonamide (see Standard Procedure (F)) in ethanol (1 mL) and 0.22 mmol tosylate derivative (e.g. 2-methyl-2-{4-[3-(toluene-4-sulfonyloxy)-propyl]-phenoxy}-propionic acid ethyl ester or 2-methyl-2-{3-[3-(toluene-4-sulfonyloxy)-propyl]-phenoxy}-propionic acid ethyl ester) in ethanol (1 mL) with approximately 50 mg potassium carbonate, were placed in a 1 dram vial and sealed. The mixture was heated at 75°C for 48 h, which was then cooled and filtered through a plug of cotton. The filtrate was charged with 0.5 mL 5N NaOH and warmed at 60°C for 2 h. After acidification with 0.7 mL 5N HCl, the crude reaction was poured onto a Varian ChemElut 1003 cartridge and eluted with 10 mL CH_2Cl_2 . After evaporation, the crude compound was purified using mass guided reverse-phase HPLC.

Example 255

Standard Procedure (C): Into a 1 dram vial was placed a solution of 0.265 mmol sulfonamide (see Standard Procedure (F)), 0.22 mmol of the appropriate bromoethyl derivative (e.g. 2-[4-(2-bromo-ethoxy)-phenoxy]-2-methyl-propionic acid ethyl ester), ethanol (1 mL), and polystyrene bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (200 mg, 2.6 mmol/g). The vial was tightly closed and heated in a block heater for 24-48 hours at 55 °C. The reaction was filtered through a plug of cotton. The filtrate was charged with 0.5 mL 5N NaOH and warmed at 60°C for 2 h. After acidification with 0.7 mL 5N HCl, the crude reaction was poured onto a Varian ChemElut 1003 cartridge and eluted with 10 mL CH_2Cl_2 . After evaporation, the crude compound was purified using mass-guided reverse phase HPLC.

30

-326-

Example 256

Standard Procedure (D): Into a 1 dram vial was placed 0.1 mmol of the appropriate aryl bromide derivative (e.g. 2-(4-{3-[(3-bromo-benzenesulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester or 2-(4-{3-[(2-bromo-benzenesulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester), 0.13 mmol of a boronic acid, 15 mg cesium fluoride, and dioxane (1 mL). About 10 mg of PdCl₂(dppf) was added, and the vials were sealed. The reactions were heated at 85°C for 18 h, which were then filtered and concentrated. The residue was dissolved in 0.8 mL ethanol, and 0.5 mL 5N NaOH were added, which was then warmed at 60°C for 2 h. After acidification with 0.7 mL 5N HCl, the crude reaction was poured onto Varian ChemElut 1003 cartridge and eluted with 10 mL CH₂Cl₂. After evaporation, the crude compound was purified using mass guided reverse-phase HPLC.

Example 257

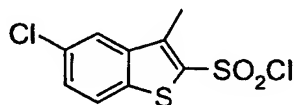
Standard Procedure (E): General sulfonyl chloride preparation

The following procedure, adopted from S.L. Graham et. al, *J. Med. Chem.*, 2548-2554 (1989), was used to prepare sulfonyl chlorides that were not commercially available. A solution of 3-methylbenzothiophene (Lancaster) (4.35g, 29.3 mmol) in THF (80 mL) was cooled to 0°C and n-BuLi (1.6M in hexanes, 21 mL, 33 mmol) was added slowly. The mixture was stirred for 15 min, and sulfonyl chloride (4.8g, 36 mmol) was added slowly while maintaining the temperature at 0°C. The mixture was warmed to ambient temperature and then shaken with ethyl acetate/water. The 3-methylbenzo[b]thiophene-2-sulfonyl chloride was purified using a flash chromatography (hexane, then 5% EtOAc/hexane) to give 1.63g (23%) product as a light yellow solid.

An alternate procedure was used to prepare some of the sulfonyl chlorides that were not commercially available.

-327-

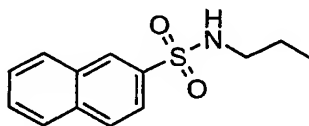
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride



A solution of chlorosulfonic acid (5.5 mL, 82.7 mmol, 3 eq.) in 1,2-dichloroethane (30 mL) at 0°C was treated dropwise over 10 min with a solution of 5-chloro-3-methyl-benzo[b]thiophene (5 g, 27.37 mmol, 1 eq.) in 1,2-dichloroethane (10 mL) while keeping the temperature at 0 to 5°C. Some solids were formed during the addition. After the addition, the purple mixture was stirred for 1 h without the cooling bath and monitored by TLC. The mixture was transferred with CH₂Cl₂ and added cautiously to 100 g of ice water with stirring. The mixture was extracted with CH₂Cl₂ (3 x 100 mL). The cloudy extract was diluted with 100 mL of MTBE until clear. The dried (Na₂SO₄) solution was concentrated to afford about 6 g (78%) of the sulfonyl chloride as an off-white solid. *R*_f = 0.45 (9.5:0.5 hexane/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ 2.80 (s, 3H), 7.56 (dd, 1H, *J* = 2.1 Hz, 8.7 Hz), 7.80 (d, 1H, *J* = 8.7 Hz), 7.90 (d, 1H, *J* = 2.1 Hz).

Example 258Standard Procedure (F): General sulfonamide preparation

Naphthalene-2-sulfonic acid propylamide



A mixture of propylamine (19 mL, 233 mmol), pyridine (19 mL, 233 mmol) and 2-naphthalenesulfonyl chloride (10.6 g, 46.8 mmol) in THF (140 mL) was stirred overnight. The mixture was quenched with water, and the THF was removed ~~under~~ reduced pressure. The residue was shaken with ethyl acetate/water. After drying (MgSO₄) the organic layer and concentration, a white solid was obtained. Trituration with hexane gave about 6.31 g (72%) white crystals (mp 76°C).

-328-

The following compounds were prepared using the standard procedure as described above:

Naphthalene-2-sulfonic acid isopropylamide; mp 115.8°C

Naphthalene-2-sulfonic acid cyclopropylamide; mp 99.9°C

5 Naphthalene-2-sulfonic acid methylamide; mp 109°C

Naphthalene-2-sulfonic acid ethylamide; mp 84.4°C

Naphthalene-2-sulfonic acid butylamide; mp 63.6°C

Naphthalene-2-sulfonic acid pentylamide; mp 72.6°C

Naphthalene-2-sulfonic acid benzylamide; mp 122.7°C

10 Naphthalene-2-sulfonic acid (2,2,2-trifluoro-ethyl)-amide; mp 187.9°C

Naphthalene-2-sulfonic acid isobutylamide; mp 118.3°C

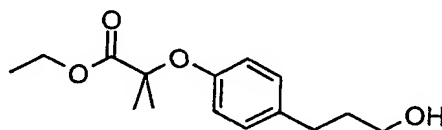
Naphthalene-2-sulfonic acid sec-butylamide; mp 122.8°C

15 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2,2,2-trifluoro-ethyl)-amide; mp 180.1°C

Example 259

Standard Synthesis of Fibrate Portion (G)

2-[4-(3-Hydroxypropyl)phenoxy]-2-methylpropanoic acid ethyl ester



20

A mixture of 3-(4-hydroxyphenyl)-1-propanol (20 g, 131.4 mmol, 1 eq.), potassium carbonate (33 g, 238.8 mmol, 1.8 eq.), and magnesium sulfate (13 g) in ethanol (260 mL) was heated to 40°C while stirring under nitrogen. Ethyl bromoisobutyrate (46 mL, 313.4 mmol, 2.4 eq.) was added. The mixture was heated to 80-81°C for 14 h. An aliquot of the mixture was periodically filtered and concentrated for HPLC (0.05% TFA, MeCN, 230 nm, 1 ml/min, Hitachi L7100). After 14 hrs, 0.61% of the starting phenol was remained. Upon cooling to room temperature, inorganic salts were removed by filtration and rinsed three times with a total of 100 mL ethanol. The filtrate was diluted with 1:1 MTBE/heptane (300 mL) and washed with water (400 mL). The aqueous layer was extracted with 1:1 MTBE/heptane (150 mL). The combined organic solution was

25

30

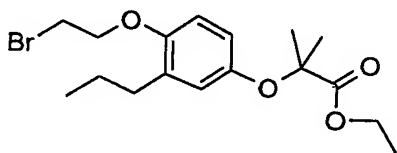
-329-

washed three times with saturated aqueous NaHCO_3 (300 mL) and once with brine (300 mL). The solution was dried (Na_2SO_4) and concentrated at a reduced pressure to afford about 32.5 g (95%) of yellow oil. R_f 0.45 (3:2 hexane/EtOAc). ^1H NMR (300 MHz, CDCl_3) δ 1.25 (t, 3H, $J = 7.2$ Hz), 1.44 (br s, 1H), 1.58 (s, 6H), 1.84 (m, 2H), 2.63 (t, 2H, $J = 7.8$ Hz), 3.65 (t, 2H, $J = 6.3$ Hz), 4.23 (q, 2H, $J = 7.2$ Hz), 6.76 (m, 2H), 7.04 (m, 2H).

Example 260

Standard Procedure (H): Bromoethoxyfibrate Preparation

2-[4-(2-Bromo-ethoxy)-3-propyl-phenoxy]-2-methyl-propionic acid ethyl ester



10

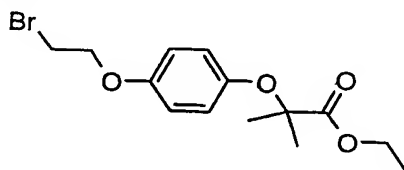
A mixture of 2-(4-hydroxy-3-propyl-phenoxy)-2-methyl-propionic acid ethyl ester (13.4 g, 50.3 mmol), Na_2SO_4 (7 g), K_2CO_3 (9.3 g, 67 mmol), 1,2-dibromoethane (65 mL, 750 mmol), and ethanol (200 mL) was refluxed for 48 h. The cooled reaction was filtered, and the solvent was removed. The residue was purified by short path filtration through 200 g silica gel using 10% ethyl acetate/hexane to give 10.2 g (54%) title compound as a pale tan oil. ^1H NMR (CDCl_3) δ 0.93 (t, 3H), 1.30 (t, 3H), 1.56 (s, 6H), 1.61 (m, 2H), 2.57 (t, 2H), 3.65 (t, 3H), 4.23 (t, 2H), 4.27 (q, 2H), 6.67 (m, 2H), 6.74 (m, 1H). MS $[\text{EI}^+]$ 375 (M+H).

15

Using the standard procedure as described above, the following compounds were prepared:

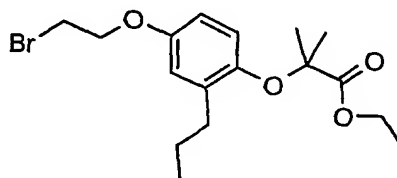
20

2-[4-(2-Bromo-ethoxy)-phenoxy]-2-methyl-propionic acid ethyl ester.

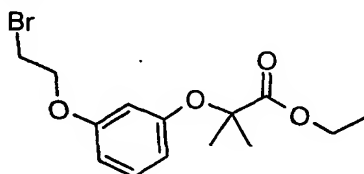


-330-

2-[4-(2-Bromo-ethoxy)-2-propyl-phenoxy]-2-methyl-propionic acid ethyl ester.



2-[3-(2-Bromo-ethoxy)-phenoxy]-2-methyl-propionic acid ethyl ester.

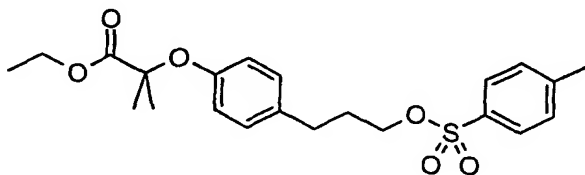


5

Example 261

Standard Procedure (I): Tosylate Preparation:

2-Methyl-2-[4-[3-[(methylphenyl)sulfonyl]oxy]propyl]phenoxy]propanoic acid ethyl ester



10

To 2-[4-(3-hydroxypropyl)phenoxy]-2-methylpropanoic acid ethyl ester (67.73 g, 0.25 mol) in dichloromethane (300 mL) at 5°C was added *p*-toluenesulfonyl chloride (53.63 g, 0.28 mol), triethylamine (39 mL, 28.13 g, 0.28 mol), and 4-dimethylaminopyridine (2.15 g, 0.026 mol). The resulting solution was held at 10°C for 6 h, and then filtered and concentrated to an oil. The oil was reconstituted in THF (300 mL) and then water (10 mL) and triethylamine (10 mL) were added. The resulting mixture was stirred at room temperature overnight. The mixture was partitioned between ethyl acetate and 1 N HCl. The organic layer was washed with saturated aqueous NaHCO₃ and NaCl, and then dried (MgSO₄), filtered and concentrated to an oil.

15

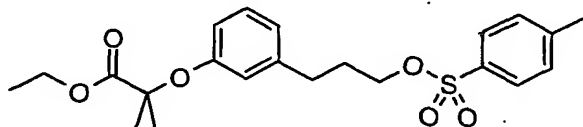
20

Purification of a 29.96 g portion of the oil was effected via silica gel chromatography (4:1 hexanes:ethyl acetate) to obtain about 17.3 g of the title compound. ¹H NMR (CDCl₃) δ 1.25 (t, 3H, *J* = 7Hz), 1.56 (s, 6H), 1.91 (m, 2H), 2.46 (s, 3H), 2.57 (t, 2H, *J* = 7Hz), 4.00

-331-

(t, 2H, J = 6 Hz, 4.23 (q, 2H, J = 7 Hz), 6.71 (d, 2H, J = 8.4 Hz), 6.91 (d, 2H, J = 8.1 Hz), 7.34 (d, 2H, J = 8.1 Hz), 7.77 (d, 2H, J = 8.4 Hz). MS [EI+] 438 (M+H+NH₃).

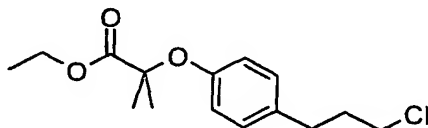
2-Methyl-2-[3-[3-[(methylphenyl)sulfonyl]oxy]propyl]phenoxy]propanoic acid ethyl ester



Using the compound of 2-[3-(3-hydroxy-propyl)-phenoxy]-2-methyl-propionic acid ethyl ester as a starting material gave the compound of 2-methyl-2-[3-[3-[(methylphenyl) sulfonyl]oxy]propyl] phenoxy]propanoic acid ethyl ester. ¹H NMR (CDCl₃) δ 1.24 (t, 3H), 1.57 (s, 6H), 1.92 (m, 2H), 2.45 (s, 3H), 2.58 (t, 2H), 4.01 (t, 2H), 4.21 (q, 2H), 6.63 (s, 1H), 6.68 (d, 1H), 7.08 (m, 1H), 7.34 (d, 2H), 7.78 (d, 2H).

The compound of 2-[4-(3-chloro-propyl)-phenoxy]-2-methyl-propionic acid ethyl ester can be used an alternative to the tosylate.

2-[4-(3-Chloro-propyl)-phenoxy]-2-methyl-propionic acid ethyl ester

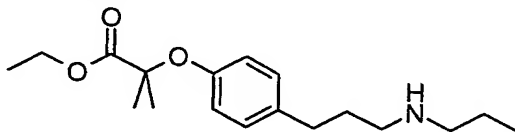


A solution of 2-[4-(3-hydroxypropyl)phenoxy]-2-methylpropanoic acid ethyl ester (34.5 g, 81% by HPLC, 0.105 mol) in 1,2-dichloroethane (142 mL) was treated dropwise but quickly with thionyl chloride (11.4 mL, 0.156 mol) and then DMF (0.1 mL) was added. The solution was stirred for 0.5 h at room temperature, heated at reflux for 1 h, and then stirred 14 h at room temperature until the starting material was consumed (as determined by TLC of concentrated aliquot). The solvent was removed at reduced pressure. The residue was taken up in MTBE (200 mL) and washed successively with 100 mL of water, saturated aqueous NaHCO₃ and brine. The dried (Na₂SO₄) solution was concentrated to afford about 36 g of title compound. R_f = 0.66 (9:1 hexanes/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ 1.25 (t, 3H, J = 7.2 Hz), 1.57 (s, 6H), 2.03 (m, 2H), 2.70 (t, 2H, J = 7.2 Hz), 3.50 (t, 2H, J = 6.6 Hz), 4.23 (q, 2H, J = 7.2 Hz), 6.77 (m, 2H), 7.05 (m, 2H).

-332-

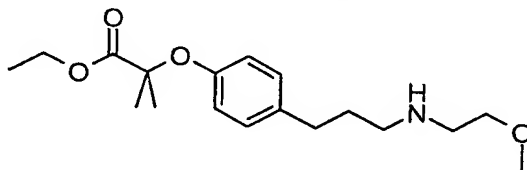
Example 262Standard Procedure (J): Fibrate Alkylamino Preparation

2-Methyl-2-[4-[3-(*n*-propylamino)propyl]phenoxy]propanoic acid ethyl ester.



5 To 2-methyl-2-[4-[3-[(methylphenyl)sulfonyl]oxy]propyl]
phenoxy]propanoic acid ethyl ester (9.81 g, 23.3 mmol) was added ethanol (75 mL) and
n-propylamine (75 mL). The resulting solution was heated at reflux for 1 h, then cooled
and concentrated to a solid. The solid was partitioned between ethyl acetate (150 mL)
and saturated aqueous NaHCO₃ (100 mL). The organic layer washed with saturated
10 aqueous NaCl (75 mL), dried (MgSO₄), filtered, and concentrated to an oil. The oil was
further purified by re-dissolving in ethyl acetate (150 mL) and by washing sequentially
with saturated aqueous NaHCO₃ (2x), water (2x), and saturated aqueous NaCl. The
organic layer was dried (MgSO₄), filtered and concentrated to afford title compound (6.22
g, 20.25 mmol, 87%) as an oil. ¹H NMR (CDCl₃) δ 0.89 (t, 3H), 1.23 (t, 3H), 1.59 (s,
15 6H), 1.62 (m, 2H), 1.91 (m, 2H), 2.59 (t, 2H), 2.69 (m, 4H), 4.22 (q, 2H), 6.76 (d, 2H),
7.02 (d, 2H). MS [EI+] 308 (M+H).

2-{4-[3-(2-Methoxy-ethylamino)-propyl]-phenoxy}-2-methyl-propionic acid ethyl ester

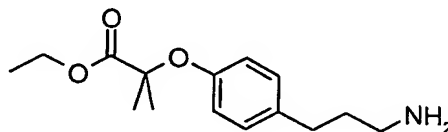


20 The title compound was prepared by following the procedure detailed
above and by using methoxyethylamine. The reaction afforded the title compound as a
light yellow oil. ¹H NMR (CDCl₃) δ 1.27 (t, 3H), 1.54 (s, 6H), 2.86 (t, 2H), 3.00 (t, 2H),
3.37 (s, 3H), 3.03 (t, 2H), 4.02 (t, 2H), 4.25 (q, 2H), 6.75 (m, 4H). MS [EI+] 326 (M+H).

25

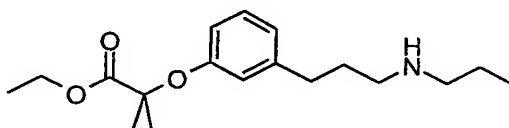
-333-

2-[4-(3-Amino-propyl)-phenoxy]-2-methyl-propionic acid ethyl ester



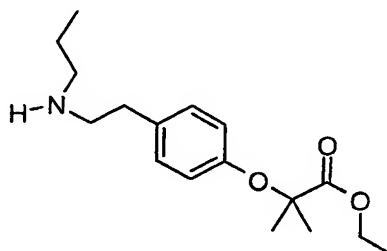
In a Carius tube was placed 2-methyl-2-[4-[3-[(methylphenyl)sulfonyl]oxy]propyl]phenoxy]propanoic acid ethyl ester (3.0 g, 7.1 mmol) and 2N NH₃/MeOH (15 mL). The tube was sealed and the solution was heated at 60°C for 20 h. The cooled solution was concentrated, and the residue was partitioned between water and ethyl acetate. After drying (MgSO₄), the solution was concentrated to yield about 1.78 g (94%) white waxy semi-solid. The product can be further purified by a flash chromatography (15% MeOH/ethyl acetate with 1% NH₄OH). ¹H NMR (DMSO-d₆) δ 1.07 (t, 3H), 1.42 (s, 6H), 1.63 (qn, 2H), 2.46 (t, 2H), 2.59 (t, 2H), 4.07 (q, 2H), 7.00 (m, 4H). MS [EI+] 266 (M+H).

2-[4-(3-Amino-propyl)-phenoxy]-2-methyl-propionic acid ethyl ester



The title compound was prepared by reacting with 2-methyl-2-[3-[3-[(methylphenyl)sulfonyl]oxy]propyl] phenoxy]propanoic acid ethyl ester by following the procedure detailed above. ¹H NMR (CDCl₃) δ 0.91 (t, 3H), 1.22 (t, 3H), 1.58 (s, 6H), 1.59 (m, 2H), 1.88 (m, 2H), 2.65 (m, 6H), 4.23 (q, 2H), 6.64 (dd, 1H), 6.69 (s, 1H), 6.81 (d, 1H), 7.12 (m, 1H).

2-Methyl-2-[4-(2-propylamino-ethyl)-phenoxy]-propionic acid ethyl ester

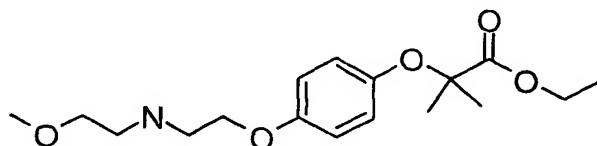


A mixture of 2-methyl-2-[4-[2-(toluene-4-sulfonyloxy)-ethyl]-phenoxy]-propionic acid ethyl ester (2.26 g, 5.35 mmol) (M. Kitazawa, et al, WO 9813333 A1

-334-

19980402) and *n*-propylamine (50 mL) in ethanol (40 mL) was stirred overnight at ambient temperature. The solution was concentrated, and the residue was partitioned between ethyl acetate/water. After drying (MgSO₄), the organic layer and the solvent was removed under reduced pressure to yield 1.36 g (87%) of the title compound as a waxy semi-solid. ¹H NMR (CDCl₃) δ 0.81 (t, 3H), 1.17 (t, 3H), 1.48 (s, 6H), 2.57 (t, 2H), 2.76 (m 4H), 3.74 (t, 2H), 4.16 (q, 2H), 6.67 (d, 2H), 6.96 (d, 2H). MS [EI+] 294 (M+H).

2-{4-[2-(2-Methoxy-ethylamino)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester.



A mixture of 2-[4-(2-bromo-ethoxy)-phenoxy]-2-methyl-propionic acid ethyl ester (2.77 g, 8.36 mmol), and 2-methoxyethylamine (10 mL) in ethanol (40 mL) was stirred at ambient temperature for 18 h. The mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and shaken with water. The organic layer was dried (MgSO₄) and concentrated to yield about 2.18 g (80%) of the title compound as a tan oil. ¹H NMR (CDCl₃) δ 1.27 (t, 3H), 1.56 (s, 6H), 2.08 (br s, 1H), 2.89 (t, 2H), 3.03 (t, 2H), 3.39 (s, 3H), 3.04 (t, 2H), 4.04 (t, 2H), 4.24 (q, 2H), 6.82 (m, 4H). MS [EI+] 326 (M+H).

Example 263

2-methyl-2-[4-[3-(*n*-propylamino)propyl]phenoxy]propanoic acid ethyl ester

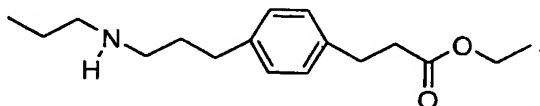
Alternately, the amines could be prepared from 2-[4-(3-chloro-propyl)-phenoxy]-2-methyl-propionic acid ethyl ester as described below.

A solution of 2-[4-(3-chloro-propyl)-phenoxy]-2-methyl-propionic acid ethyl ester (36 g, 0.126 mol) in 1:1 EtOH/propylamine (144 mL) was heated at reflux for 24 h under nitrogen until starting material was consumed. After cooling to room temperature, the solvent was removed at reduced pressure. The residual oil was taken up in 1:1 EtOAc/heptane (300 mL) and washed three times with 200 mL of 10% aqueous K₂CO₃, and then with 200 mL brine. The dried (Na₂SO₄) solution was concentrated to afford about 38.2 g (98%) of 2-methyl-2-[4-[3-(*n*-propylamino)propyl]phenoxy]propanoic acid

-335-

ethyl ester as yellow oil. R_f 0.52 (8.9:1.1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). ^1H NMR (300 MHz, CDCl_3) δ 0.89 (t, 3H, $J = 7.2$ Hz), 1.24 (t, 3H, $J = 7.2$ Hz), 1.47 (m, 3H), 1.56 (s, 6H), 1.77 (m, 2H), 2.57 (m, 6H), 4.22 (q, 2H, $J = 7.2$ Hz), 6.75 (m, 2H), 7.03 (m, 2H).

5 3-[4-(3-Propylamino-propyl)-phenyl]-propionic acid methyl ester.



Step A

3-[4-(3-hydroxy-prop-1-ynyl)-phenyl]-propionic acid methyl ester

Under argon, in a flame dried flask, was placed 3-(4-
 10 trifluoromethanesulfonyloxy-phenyl)-propionic acid methyl ester (1.0 g, 7.2 mmol) (G.R. Brown et al, WO 94-GB910 19940428, CAS [166959-38-2]), propargyl alcohol (1.12 mL, 19.2 mmol) and DMF (6 mL). Lastly, triethylamine (1.78 mL, 12.8 mmol) and $\text{Pd}(\text{Ph}_3\text{P})\text{Cl}_2$ (112 mg, 0.16 mmol) were added. The reaction was heated at 90°C for 2 h and then cooled and concentrated under vacuum. The residue was diluted with ethyl
 15 acetate (200 mL) and brine (100 mL). The aqueous layer was extracted a second time with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated to give 1.1 g crude product as a dark oil. The product was purified by a radial chromatography using a gradient of 25-35% EtOAc/hexanes. The pure fractions were concentrated to yield about 0.29 g (42%) of 3-[4-(3-hydroxy-prop-1-ynyl)-phenyl]-
 20 propionic acid methyl ester as a yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 2.62 (t, 2H), 2.94 (t, 2H), 3.66 (s, 3H), 4.49 (d, 2H), 7.14 (d, 2H), 7.30 (d, 2H). MS [EI] 218 (M).

Step B

3-[4-(3-hydroxy-propyl)-phenyl]-propionic acid methyl ester

25 The compound of 3-[4-(3-hydroxy-prop-1-ynyl)-phenyl]-propionic acid methyl ester (1.0 g, 4.58 mmol) was dissolved in THF (20 mL), and 10% Pd/C (100 mg) was added. The slurry was stirred under a hydrogen atmosphere for 16 h, and then filtered through Celite and concentrated to give about 0.97 g (95%) of 3-[4-(3-hydroxy-propyl)-phenyl]-propionic acid methyl ester as an off-white solid. ^1H NMR (CDCl_3) δ
 30 1.25 (br s, 1H). 1.88 (m, 2H), 2.64 (m, 4H), 2.92 (t, 2H), 3.67 (s and m, 5H). 7.12 (s, 4H). MS [EI+] 223 (M+1).

-336-

Step C

3-[4-(3-benzenesulfonyloxy-propyl)-phenyl]-propionic acid methyl ester

A mixture of 3-[4-(3-hydroxy-propyl)-phenyl]-propionic acid methyl ester (0.95 g, 4.27 mmol), DMAP (0.156 g, 1.28 mmol), tosic anhydride (1.67 g, 5.12 mmol), pyridine (1.17 mL), and dichloromethane (17 mL) was stirred at ambient temperature for 18h. The reaction was charged with 1N HCl (16 mL), stirred vigorously for 1 h, and then the layers were separated. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated to give about 1.6 g (100%) of 3-[4-(3-benzenesulfonyloxy-propyl)-phenyl]-propionic acid methyl ester as a colorless oil. ¹H NMR (CDCl₃) δ 1.93 (qn, 2H), 2.46 (s, 3H), 2.60 (m, 4H), 2.90 (t, 2H), 3.66 (s, 3H), 4.02 (t, 2H), 7.00 (d, 2H), 7.07 (d, 2H), 7.33 (d, 2H), 7.79 (d, 2H). MS [EI+] 377 (M+1).

Step D

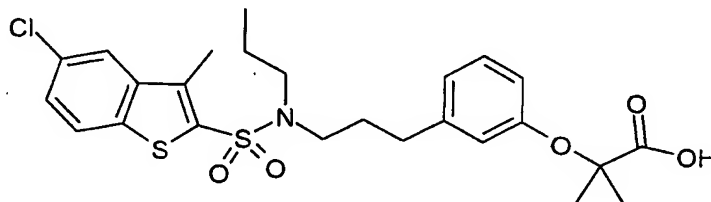
3-[4-(3-propylamino-propyl)-phenyl]-propionic acid methyl ester

A solution of 3-[4-(3-benzenesulfonyloxy-propyl)-phenyl]-propionic acid methyl ester (1.82 mL, 4.83 mmol) in DMF (54 mL) and n-propylamine (1.99 mL, 24.2 mmol) was stirred at room temperature for 18h. The reaction was partitioned between water (50 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated to give about 1.3 g (100%) of 3-[4-(3-propylamino-propyl)-phenyl]-propionic acid methyl ester as a thin oil. ¹H NMR (CDCl₃) δ 0.91 (t, 3H), 1.84 (m, 2H), 2.20 (qn, 2H), 2.61 (m, 4H), 2.90 (m, 6H), 3.66 (s, 6H), 7.26 (s, 4H), 9.40 (br s, 1H). MS [EI+] 264 (M+1).

-337-

Example 264

2-(3-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid.



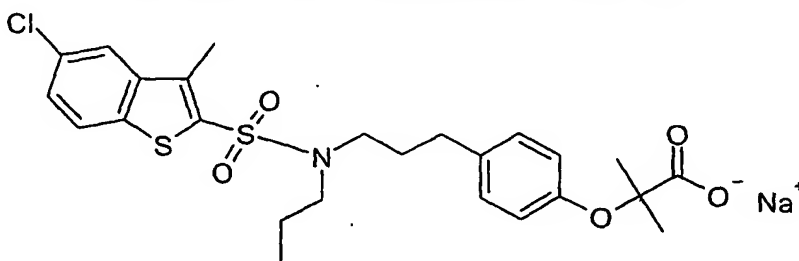
5 A mixture of 2-methyl-2-[3-(3-propylamino-propyl)-phenoxy]-propionic acid ethyl ester (550 mg, 1.79 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (503 mg, 1.79 mmol) and 3 mL triethylamine was dissolved in 40 mL dichloromethane and stirred for 18 h at room temperature. The reaction was shaken with dilute HCl, dried (MgSO₄) and concentrated to give 750 mg crude product. The ester was
10 purified by a flash chromatography using 12% EtOAc/hexane. After concentration of the fractions containing pure product, about 390 mg (39%) ester was obtained as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 0.80 (t, 3H), 1.17 (t, 3H), 1.45 (m, 2H), 1.51 (s, 6H), 1.79 (m, 2H), 2.47 (t, 2H), 2.55 (s, 3H), 3.13 (m, 4H), 4.14 (q, 2H), 6.55 (m, 2H), 6.67 (br d, 1H), 7.04 (t, 1H), 7.36 (dd, 1H), 7.66 (m, 2H). MS [EI+] 552 (M+H), 569 (M+NH₃).

15 The ester obtained above (390 mg, 0.71 mmol) was dissolved in EtOH (10 mL), and then 5 N NaOH (5 mL) was added. The solution was warmed at 50°C for 1.5 h. The cooled hydrolysis reaction was concentrated to remove most of the ethanol, acidified with HCl, and extracted with ethyl acetate. The organic layer was dried (MgSO₄) and concentrated to give 275 mg (74%) of the title compound as a light pink oil, which slowly
20 crystallized. ¹H NMR (300 MHz, CDCl₃) δ 0.94 (t, 3H), 1.60 (m, 2H), 1.55 (s, 6H), 1.94 (m, 2H), 2.65 (t, 2H), 2.67 (s, 3H), 3.27 (m, 4H), 6.85 (m, 3H), 7.22 (m, 1H), 7.48 (dd, 1H), 7.79 (m, 2H). MS [ES+] 524 (M+H), [EI-] 522 (M-H).

-338-

Example 265

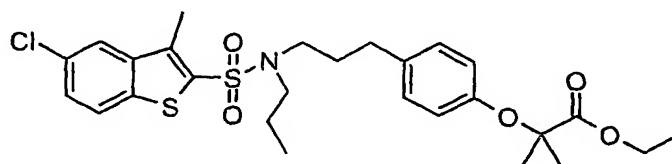
2-(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionate, sodium salt.



5

Step A

2-(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester.

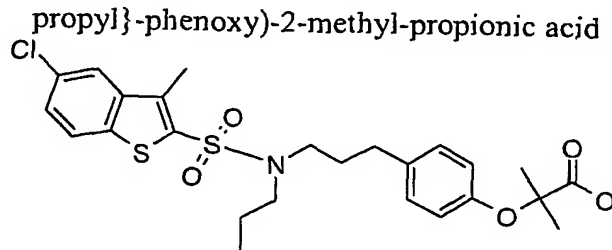


A mixture of 2-methyl-2-[4-(3-propylamino-propyl)-phenoxy]-propionic acid ethyl ester (2.25 g, 7.3 mmol), 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (2.06 g, 7.3 mmol), triethylamine (5 mL) and dichloromethane (50 mL) was stirred for 18 h. at room temperature. The mixture was shaken with 1N HCl, dried (MgSO₄) and concentrated to give 3.3 g crude product. The ester was purified by a flash chromatography (15% ethyl acetate/hexane) to yield 990 mg of pure ester. ¹H NMR (300 MHz, CDCl₃): δ 0.79 (t, 3H), 1.17 (t, 3H), 1.47 (m, 2H), 1.49 (s, 6H), 1.78 (m, 2H), 2.46 (t, 2H), 3.12 (q, 2H), 4.15 (q, 2H), 6.66 (d, 2H), 6.91 (d, 2H), 7.36 (dd, 1H), 7.65 (m, 3H). MS [EI+] 552 (M+H), 569 (M+NH₃).

-339-

Step B

2-(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid

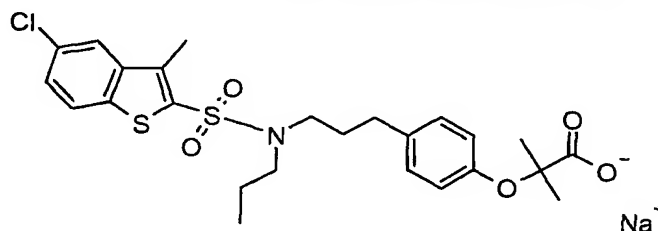


5 A solution of 2-(4-{3-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester (990 mg, 1.79 mmol) in ethanol (30 mL) was treated with 5N NaOH (3 mL) and warmed at 50°C for 2 h. The cooled mixture was diluted with water and most of the ethanol was removed under reduced pressure. After acidification with aqueous HCl, the product was extracted
10 into ethyl acetate. The organic layer was dried (MgSO₄) and concentrated to give 810 mg (86%) of the title compound as a viscous oil. ¹H NMR (300 MHz, CDCl₃): δ 0.82 (t, 3H), 1.48 (s, 6H), 1.49 (m, 2H), 1.81 (m, 2H), 2.52 (m, 2H), 2.56 (s, 3H), 3.18 (m, 4H), 6.78 (d, 2H), 7.00 (d, 2H), 7.37 (dd, 1H), 7.66 (m, 3H). MS [EI+] 524 (M=H), [EI-] 522 (M-H)

15

Step C

2-(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionate, sodium salt



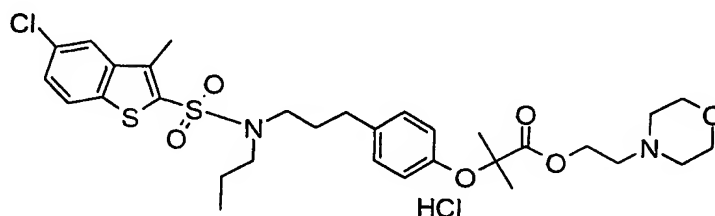
A solution of 2-(4-{3-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic (80mg, 0.15 mmol) in ethyl acetate
20 (1 mL) under nitrogen was treated with sodium 2-ethylhexanoate (28 mg, 0.17 mmol), and the reaction was stirred at room temperature. After 8 h, the precipitate was collected and dried to give 71 mg (87%) of the title compound as an off-white solid. ¹H NMR (300 MHz, DMSO-d₆): δ 0.81 (t, 3H), 1.35 (s, 6H), 1.49 (m, 2H), 1.72 (m, 2H), 2.42 (t, 2H),

-340-

2.58 (s, 3H), 3.17 (m, 4H), 6.70 (d, 2H), 6.87 (d, 2H), 7.59 (dd, 1H), 8.06 (d, 1H), 8.15 (d, 1H). MS [EI+] 524 (M+H), [EI-] 522 (M-H).

Example 266

- 5 2-(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid 2-morpholin-4-yl-ethyl ester, HCl salt.



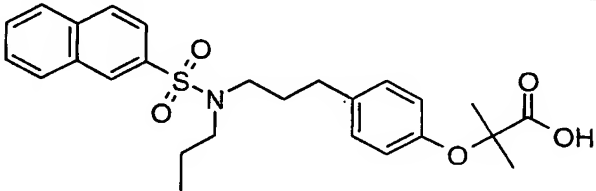
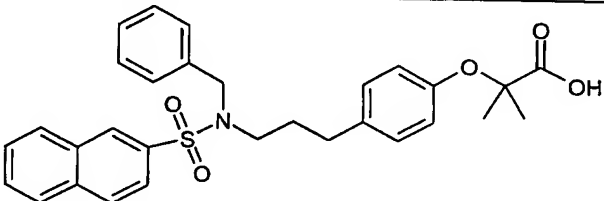
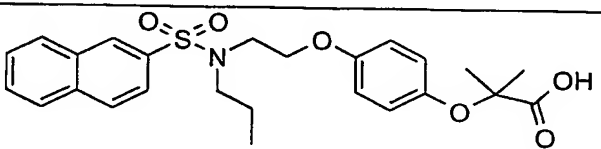
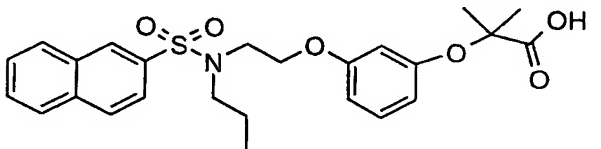
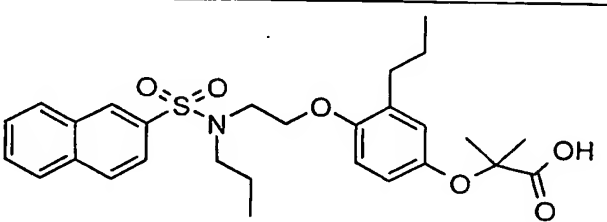
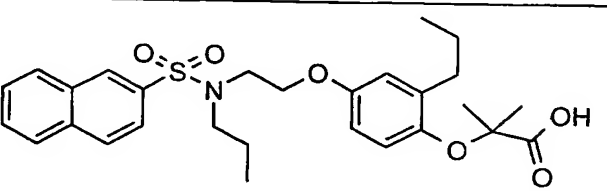
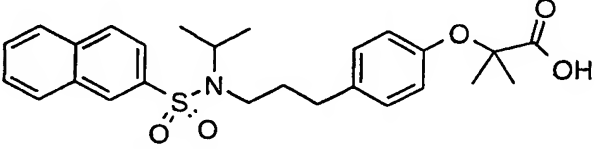
- 10 2-(4-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-phenoxy)-2-methyl-propionic acid (330 mg, 0.63 mmol) was dissolved in dichloromethane (3 mL), and 2M oxalyl chloride in CH₂Cl₂ (400 μL, 0.8 mmol) was added. One drop of DMF was added, and the reaction was stirred for 1 h. The mixture was concentrated and the residue was redissolved in CH₂Cl₂. The compound of 2-(2-hydroxyethyl)morpholine (121 μL, 1 mmol), triethylamine (131 μL, 1 mmol), and a catalytic amount of DMAP were added. The mixture was stirred for 18 h, concentrated, and purified by a flash chromatography (60% ethyl acetate/hexane). The colorless oil (180 mg) was dissolved in diethyl ether, and 1M HCl/ether (500 μL) was added. The resulting oil was dissolved in EtOAc, and the solution was concentrated. The residue was dissolved in dichloromethane, and the mixture was concentrated to yield 124 mg (31%) of the title compound as a white hygroscopic foam. ¹H NMR (300 MHz, CDCl₃): δ 0.8 (t, 3H), 1.50 (m, 6H), 1.54 (s, 6H), 1.81 (m, 2H), 2.47 (m, 2H), 2.55 (s, 3H), 3.05 (m, 2H), 3.14 (m, 4H), 3.65 (m, 2H), 4.01 (m, 2H), 4.67 (m, 2H), 6.62 (d, 2H), 6.95 (d, 2H), 7.37 (dd, 1H), 7.66 (m, 3H), 13.35 (br s, 1H). MS [EI+] 637 (M+H).
- 15
- 20

25

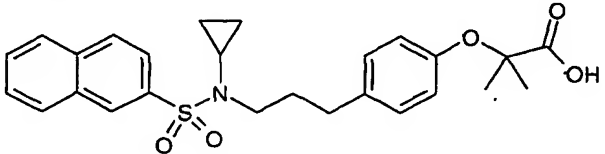
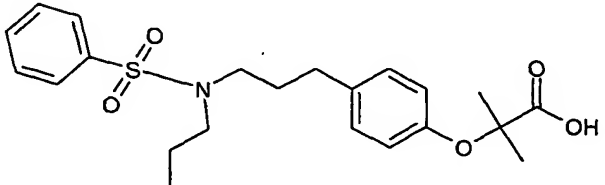
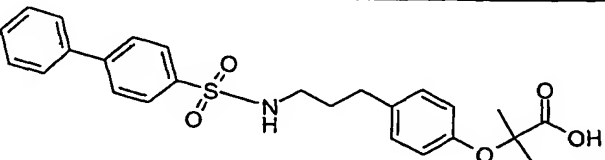
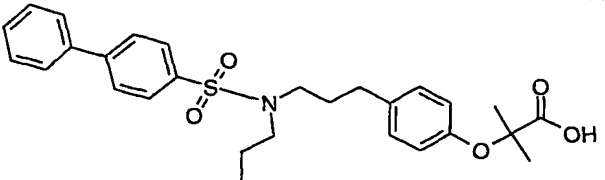
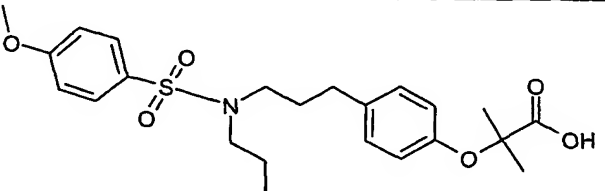
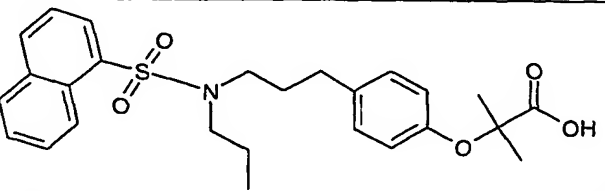
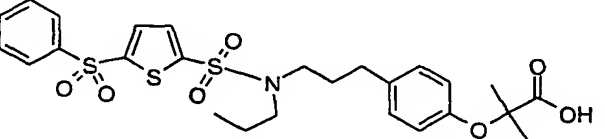
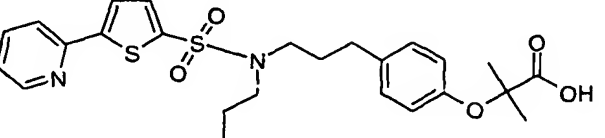
-341-

Examples 267 - 385

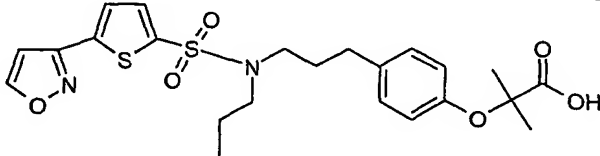
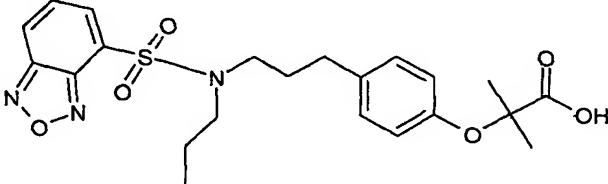
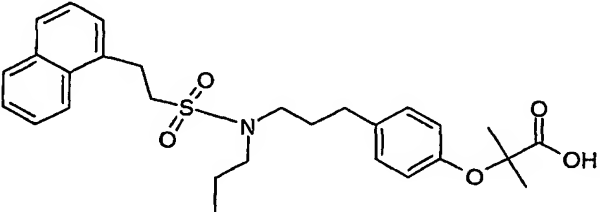
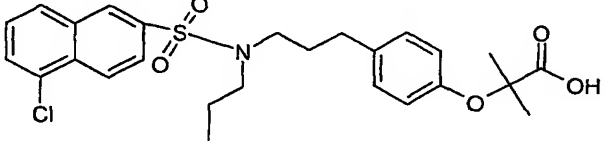
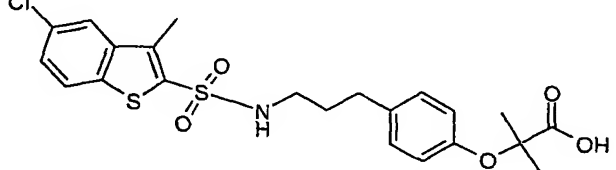
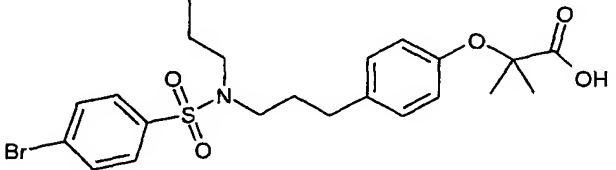
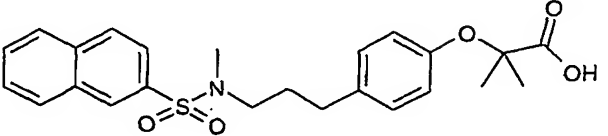
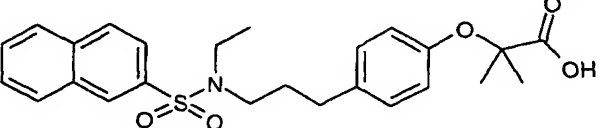
Examples 267 to 385 were prepared according to the indicated Standard Procedures as described in Examples 253 to 262.

Example No.	Structure	MS(ES)	Standard Procedure
267		M+H=270 M-H=468	A
268		M+H=518 M-H=516	C
269		M+H=472 M-H=470	C
270		M+H=472 M-H=470	C
271		M+H=514 M-H=512	C
272		M+H=514 M-H=512	C
273		M+H=470 M-H=469	B

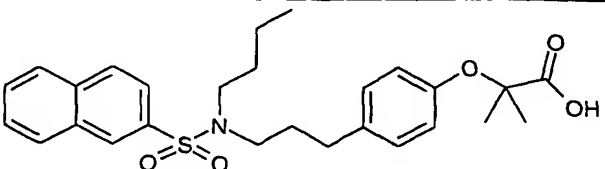
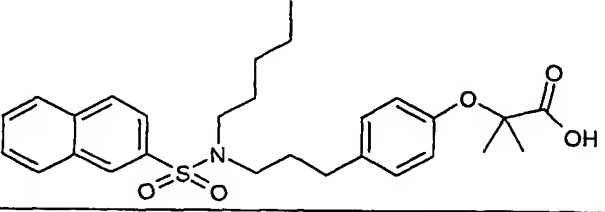
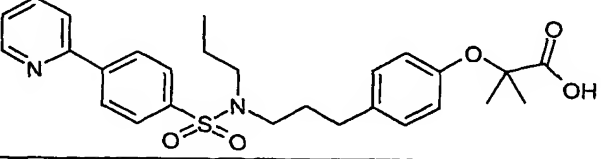
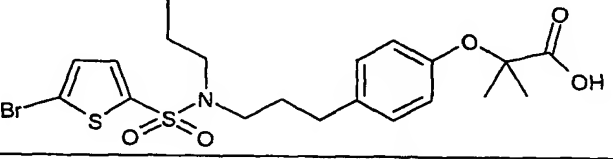
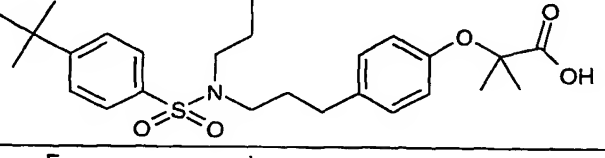
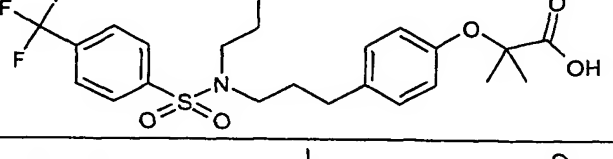
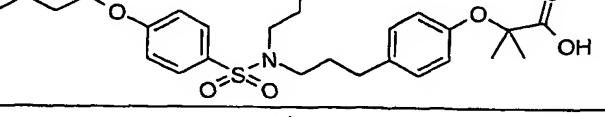
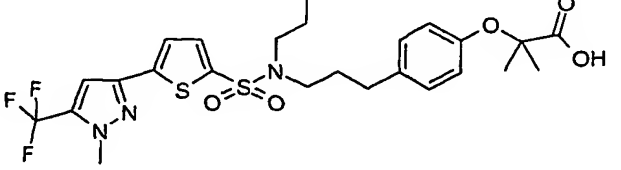
-342-

Example No.	Structure	MS(ES)	Standard Procedure
274		M+H=420 M-H=418	B
275		M+H=454 M-H=452	A
276		M+H=468 M-H=466	A
277		M+H=469 M-H=494	A
278		M+H=450 M-H=448	A
279		M+H=470 M-H=468	A
280		M+H=566 M-H=564	A
281		M+H=503 M-H=501	A

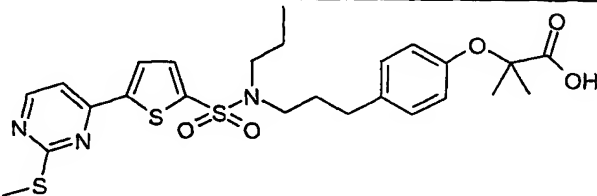
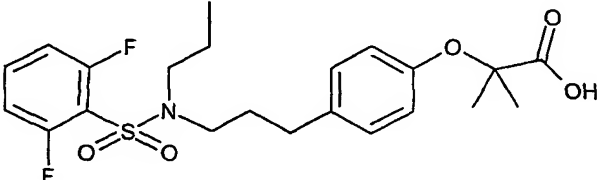
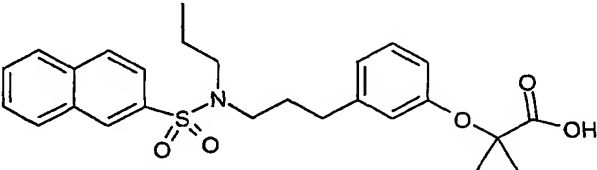
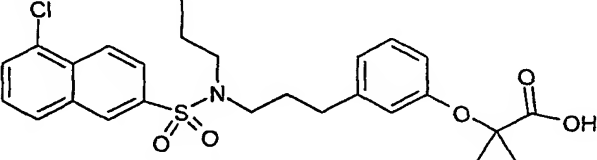
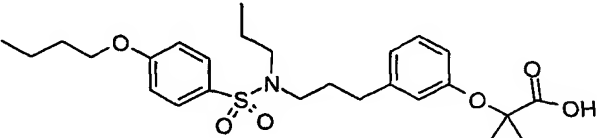
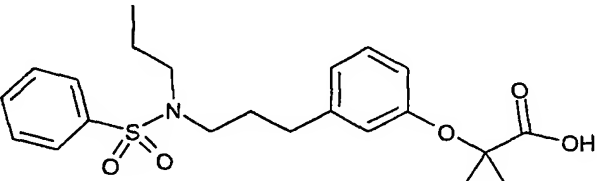
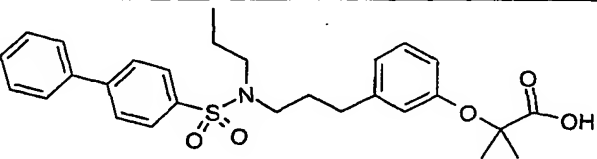
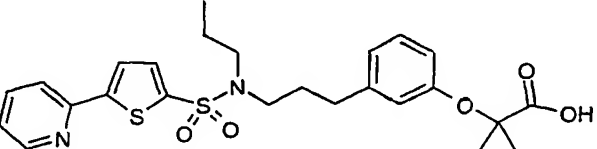
-343-

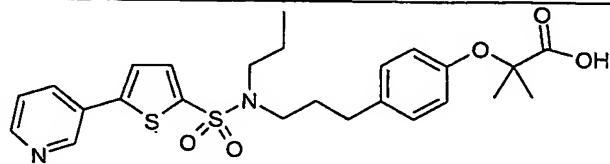
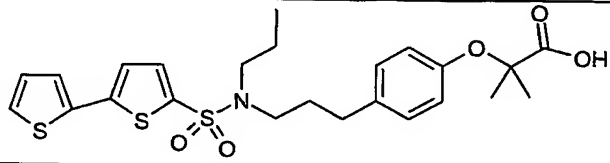
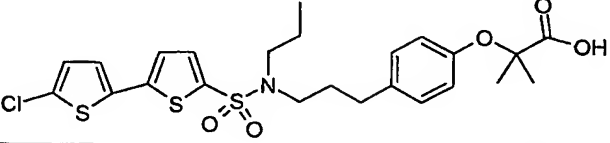
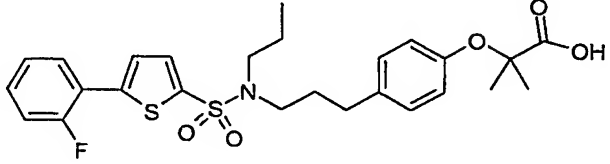
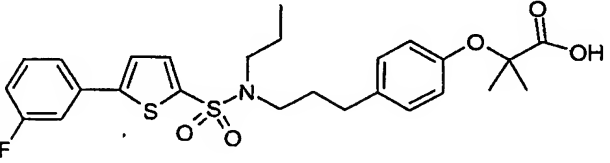
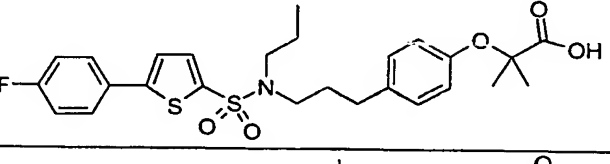
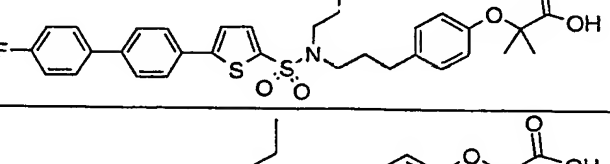
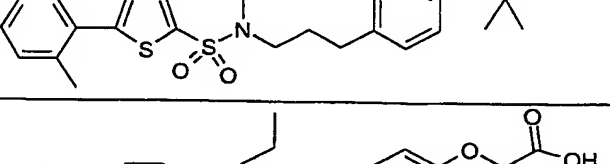
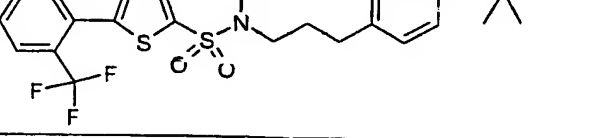
Example No.	Structure	MS(ES)	Standard Procedure
282		M+H=493 M-H=491	A
283		M+H=462 M-H=460	A
284		M+H=498 M-H=496	A
285		M+H=504 M-H=502	A
286		M+H=482 M-H=480	A
287		M+H=500 M-H=498	A
288		M+H=442 M-H=440 =440	B
289		M+H=456 M-H=454	B

-344-

Example No.	Structure	MS(ES)	Standard Procedure
290		M+H=484 M-H=482	B
291		M+H=498 M-H=496	B
292		M+H=497 M-H=495	D
293		M+H=506 M-H=504	A
294		M+H=476 M-H=474	A
295		M+H=488 M-H=486	A
296		M+H=492 M-H=490	A
297		M+H=574 M-H=572	A

-345-

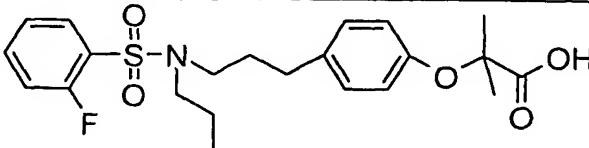
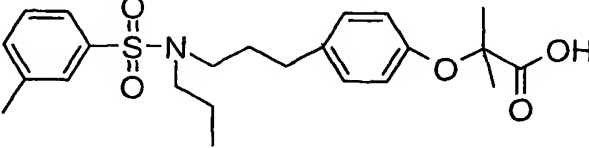
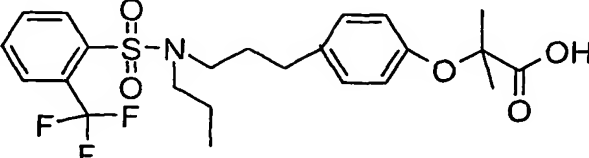
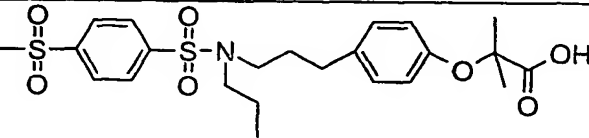
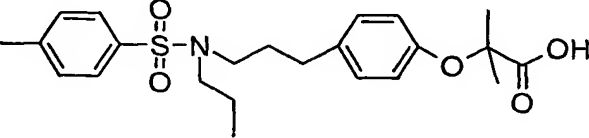
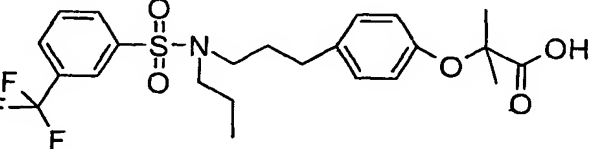
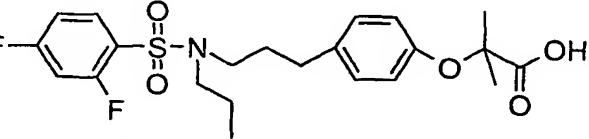
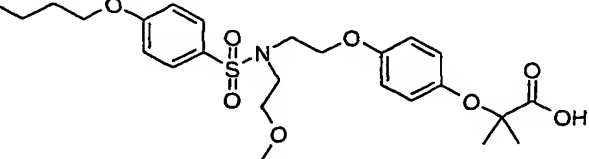
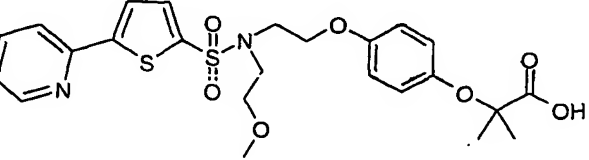
Example No.	Structure	MS(ES)	Standard Procedure
299		M+H=550 M-H=548	A
299		M+H=456 M-H=454	A
300		M+H=470 M-H=468	A
301		M+H=504 M-H=502	A
302		M+H=492 M-H=490	A
303		M+H=450 M-H=448	A
304		M+H=496 M-H=494	A
305		M+H=503 M-H=501	A

Example No.	Structure	MS(ES)	Standard Procedure
306		M+H=503 M-H=501	D
307		M+H=508 M-H=506	D
308		M+H=542 M-H=540	D
309		M+H=520 M-H=518	D
310		M+H=520 M-H=518	D
311		M+H=520 M-H=518	D
312		M+H=596 M-H=594	D
313		M+H=516 M-H=514	D
314		M+H=570 M-H=568	D

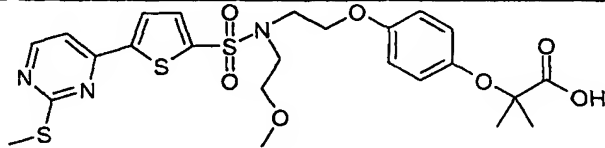
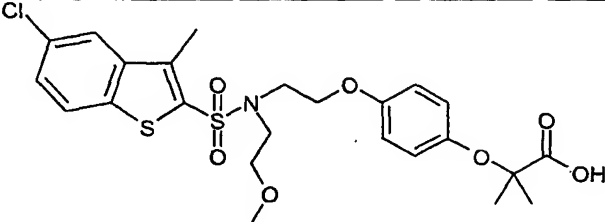
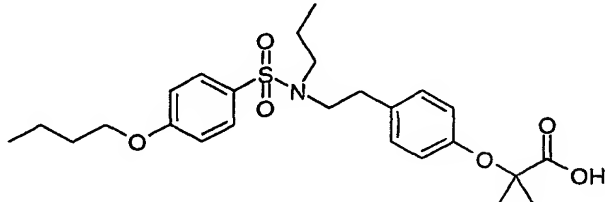
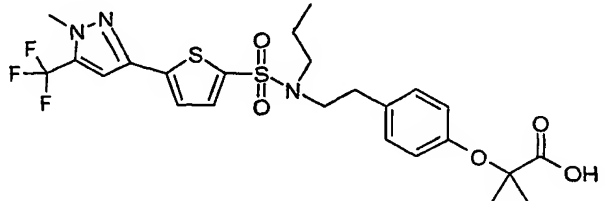
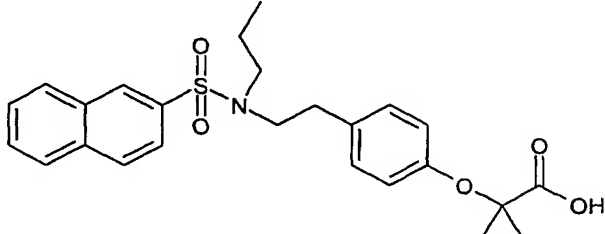
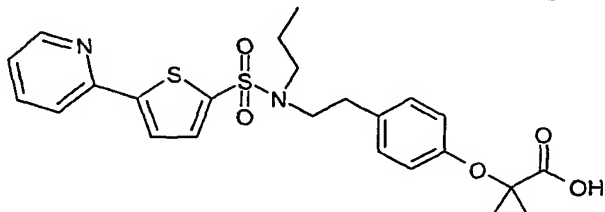
-347-

Example No.	Structure	MS(ES)	Standard Procedure
315		M+H=570 M-H=568	D
316		M+H=503 M-H=501	D
317		M+H=500 M-H=498	A
318		M+H=490 M-H=488	A
319		M+H=490 M-H=488	A
320		M+H=504	A
321		M+H=462	A
322		M+H=465	A

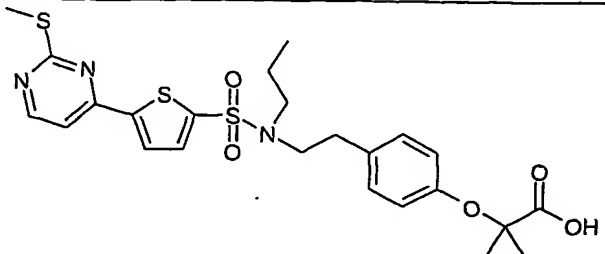
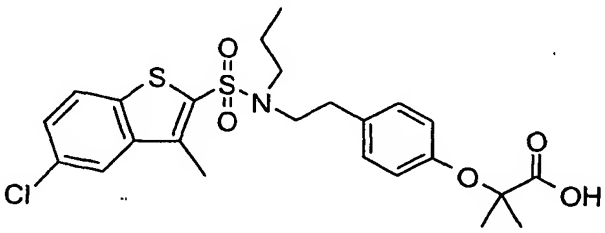
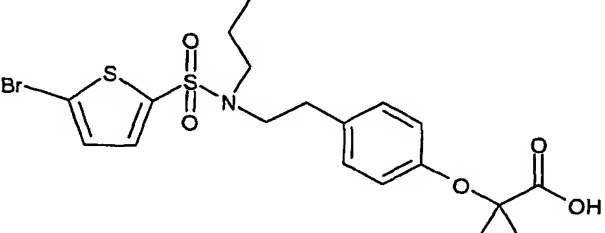
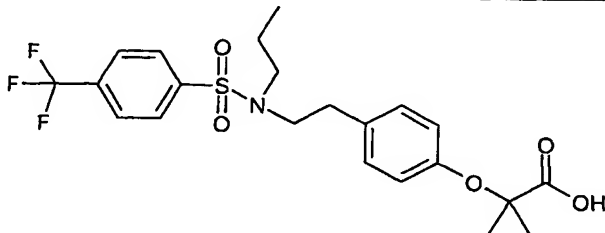
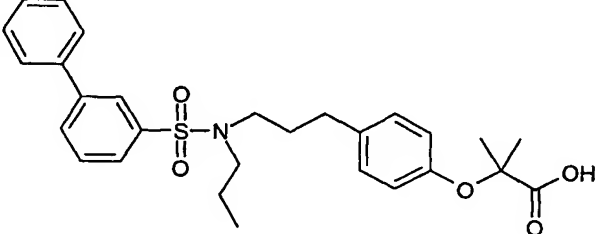
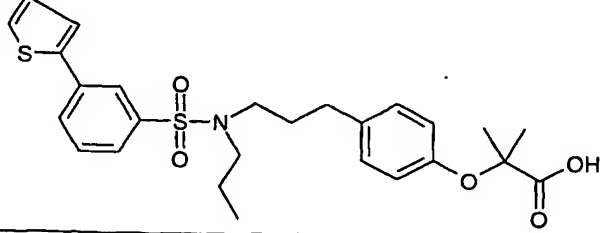
-348-

Example No.	Structure	MS(ES)	Standard Procedure
323		M+H=438	A
324		M+H=434	A
325		M+H=488	A
326		M+H=498	A
327		M+H=434	A
328		M+H=488	A
329		M+H=456	A
330		M+H=510 M-H=508	A
331		M+H=521 M-H=519	A

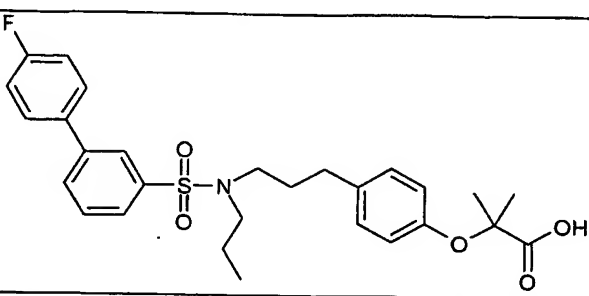
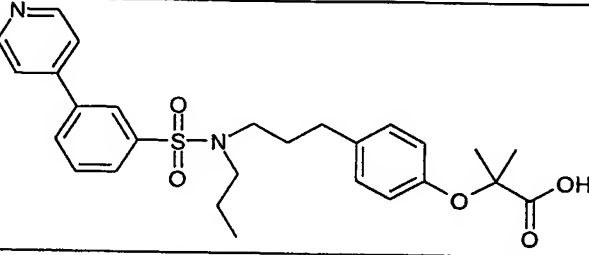
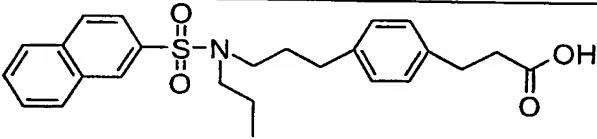
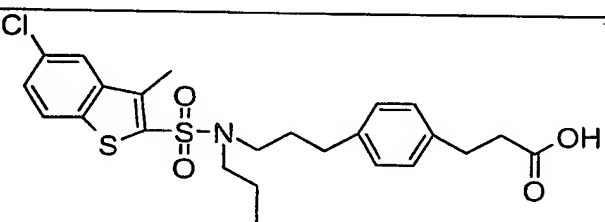
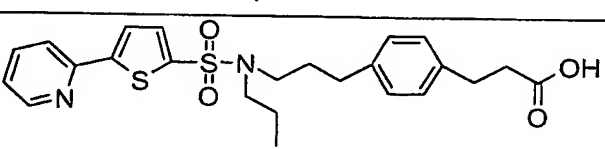
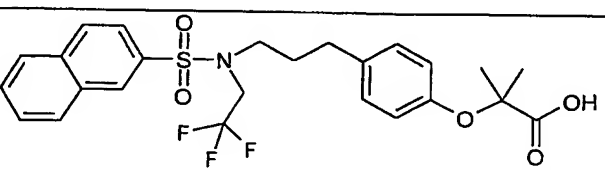
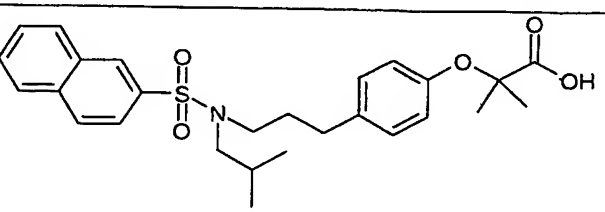
-349-

Example No.	Structure	MS(ES)	Standard Procedure
332		M+H=568 M-H=566	A
333		M+H=542 M-H=540	A
334		M+H=478 M-H=476	A
335		M+H=550 M-H=558	A
336		M+H=456 M-H=454	A
337		M+H=489 M-H=487	A

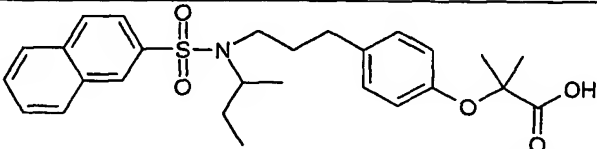
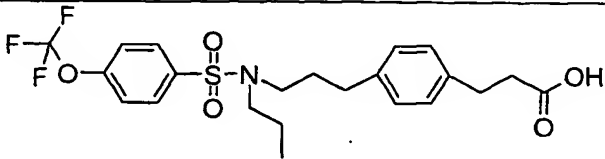
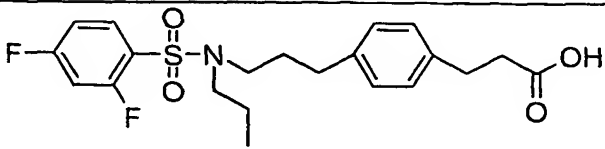
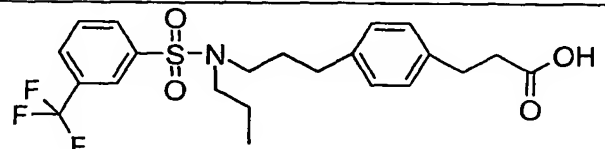
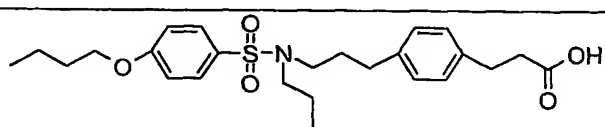
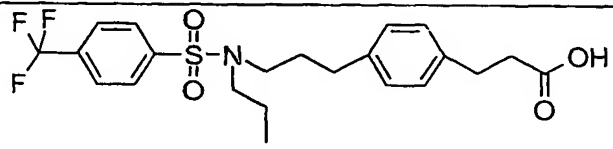
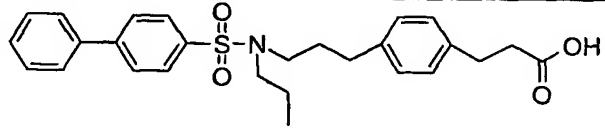
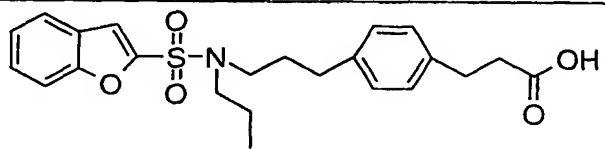
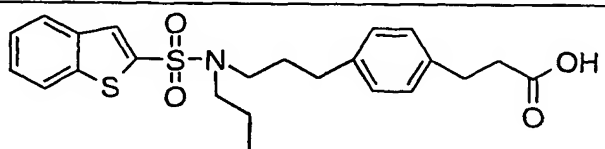
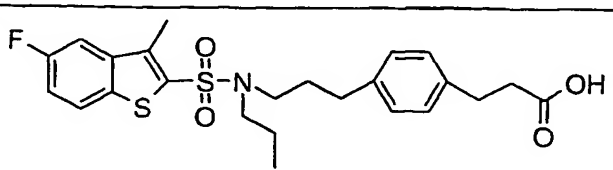
-350-

Example No.	Structure	MS(ES)	Standard Procedure
338		M+H=536 M-H=534	A
339		M+H=510 M-H=508	A
340		M+H=492 M-H=490	A
341		M+H=474 M-H=472	A
342		M+H=496 M-H=494	D
343		M+H=500 M-H=498	D

-351-

Example No.	Structure	MS(ES)	Standard Procedure
344		M+H=514 M-H=512	D
345		M+H=497 M-H=495	D
346		M+H=440	A
347		M+H=495	A
348		M+H=473	A
349		M+H=510 M-H=508	B
350		M+H=484 M-H=482	B

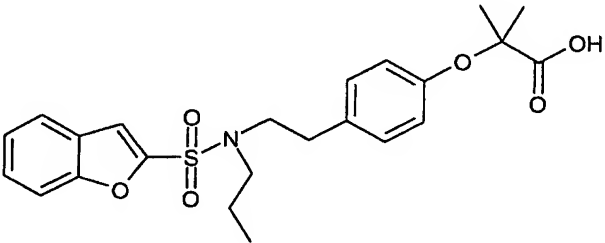
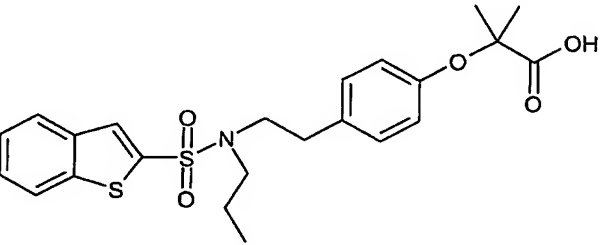
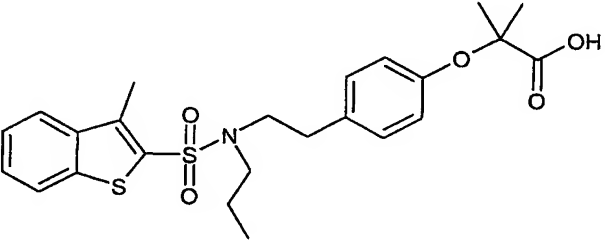
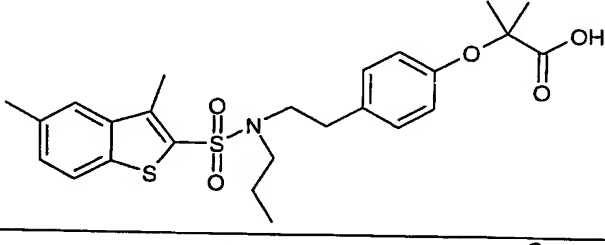
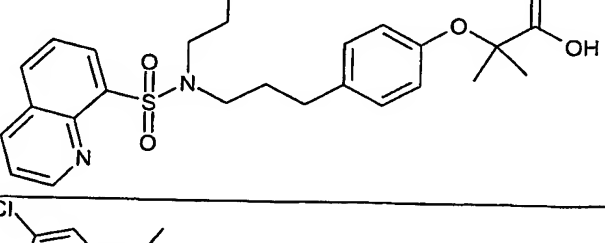
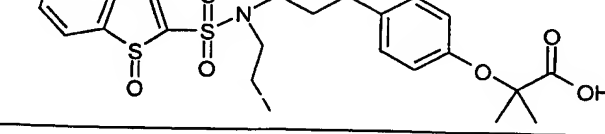
-352-

Example No.	Structure	MS(ES)	Standard Procedure
351		M+H=484 M-H=482	B
352		M+H=474	A
353		M+H=426	A
354		M+H=458	A
355		M+H=462	A
356		M+H=458	A
357		M+H=466	A
358		M+H=430	A
359		M+H=446	A
360		M+H=478	A

-353-

Example No.	Structure	MS(ES)	Standard Procedure
361		M+H=460 M-H=458	A
362		M+H=476 M-H=474	A
363		M+H=504 M-H=502	A
364		M+H=508 M-H=506	A
365		M+H=460 M-H=458	A
366		M+H=476 M-H=474	A
367		M+H=490 M-H=488	A
368		M+H=504 M-H=502	A
369		M+H=508 M-H=506	A

-354-

Example No.	Structure	MS(ES)	Standard Procedure
370		M+H=446 M-H=444	A
371		M+H=462 M-H=460	A
372		M+H=476 M-H=474	A
373		M+H=490 M-H=488	A
374		M+H=471 M-H=469	A
375		M+NH3=557	MCPBA oxidation

-355-

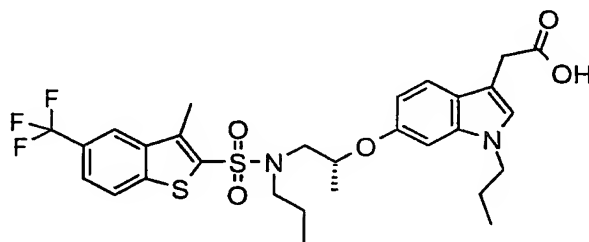
Example No.	Structure	MS(ES)	Standard Procedure
376		M+H=557 M-H=554	MCPBA oxidation
377		M+NH3=567 M-H=548	B
378		M+NH3=551 M-H=562	B
379		M+NH3=581 M-H=562	B
380		M+NH3=565 M-H=546	A
381		M+NH3=521 M-H=502	A
382		M+NH3=537 M-H=518	A

-356-

Example No.	Structure	MS(ES)	Standard Procedure
383		M+NH ₃ = 539 M-H=520	A
384		M+NH ₃ = 479 M-H=460	A
385		M+NH ₃ = 521 M-H=502	A

Example 386

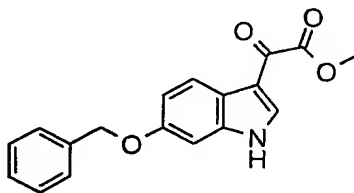
(R)-(6-{1-Methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-1-propyl-1H-indol-3-yl)-acetic acid



5

Step A

(6-Benzyloxy-1H-indol-3-yl)-oxo-acetic acid methyl ester



To a solution of 6-benzyloxyindole (25 g, 112 mmol) in diethylether (300 mL) was added oxalyl chloride (10.7 mL, 123 mmol) at 0~5 °C, and the mixture was stirred for 2 hrs. The mixture was cooled to -78 °C. and sodium methoxide (25 %w/w in methanol, 31 mL) was added over one hour. The mixture was warmed to room

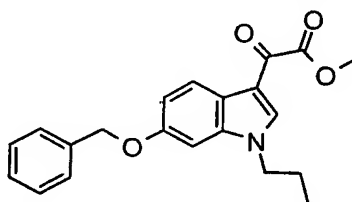
10

-357-

temperature, and then quenched with water. The solid product is collected by filtration, washed with water and dried under vacuum.

Step B

(6-Benzyloxy-1-propyl-1H-indol-3-yl)-oxo-acetic acid methyl ester



5

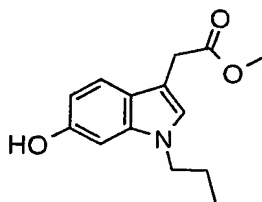
To a solution of (6-benzyloxy-1H-indol-3-yl)-oxo-acetic acid methyl ester (3.0 g, 9.7 mmol) in anhydrous dimethyl formamide (50 mL) at 0°C under nitrogen was added sodium hydride (0.600 g, 14.5 mmol) in small portions. The reaction was allowed to warm to room temperature and stirred for 2 hours. The mixture was cooled to 0°C and n-propyl iodide (1.9 mL, 20 mmol) was slowly added to the slurry. The reaction was allowed to warm slowly to room temperature and monitored by TLC. After complete consumption of the starting material, the reaction was quenched with water, then diluted with ethyl acetate, and the two phases were separated. The organic layer was washed, dried, filtered and concentrated. The crude (6-benzyloxy-1-propyl-1H-indol-3-yl)-oxo-acetic acid ethyl ester (0.840 g, 2.20 mmol), 25% yield, was further purified using flash column chromatography.

10

15

Step C

(6-Hydroxy-1-propyl-1H-indol-3-yl)-acetic acid methyl ester



20

The compound of (6-benzyloxy-1-propyl-1H-indol-3-yl)-oxo-acetic acid methyl ester (0.810 g, 2.20 mmol) was dissolved in anhydrous dioxane (10 mL) and 10% palladium on carbon (200 mg) was added. The mixture was purged and back filled with nitrogen several times, and then replaced with an atmosphere of hydrogen. The reaction mixture was heated to reflux and a saturated solution of sodium hypophosphite (1 mL) was added over one hour, and then the mixture heated at reflux temperature overnight. After

25

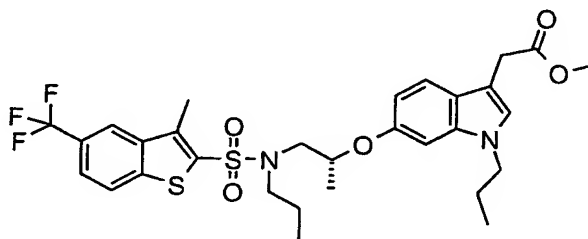
-358-

the starting material was completely consumed, the reaction was allowed to cool to room temperature, diluted with dichloromethane and celite was added. The mixture was filtered through a plug of celite and the two phases were separated. The organic layer was washed with water and brine, and dried over sodium sulfate and then concentrated.

5 The residue was purified using flash column chromatography to afford the title compound.

Step D

(R)-(6-{1-Methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-1-propyl-1H-indol-3-yl)-acetic acid methyl ester



10

To a cooled solution of (6-hydroxy-1-propyl-1H-indol-3-yl)-acetic acid methyl ester (112 mg, 0.45 mmol) and (S)-3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonic acid (2-hydroxy-propyl)-propyl-amide (150 mg, 0.37 mmol) in toluene (2 ml) at 0°C was added tri-n-butylphosphine (0.11 ml, 0.45 mmol) over 1 minute followed by the dropwise addition of a solution of 1.1'-(azodicarbonyl) dipiperidine (113 mg, 0.45 mmol) in toluene (1.5 ml) over 5 minutes. The suspension was stirred in at 0°C for 15 minutes, and then stirred at room temperature for 18 hours. The mixture was diluted with hexanes (4 ml), filtered, and the filtrate was concentrated to give an oil. Purification by silica chromatography using 8:1 hexanes:ethyl acetate

15

20 provided the title compound as an oil, 33 mg.

Step E

(R)-(6-{1-Methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-1-propyl-1H-indol-3-yl)-acetic acid

To a solution of (R)-(6-{1-methyl-2-[(3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-1-propyl-1H-indol-3-yl)-acetic acid methyl ester (33 mg, 0.052 mmol) in methanol (2 ml) at room temperature was added aqueous 5N NaOH (0.5 ml, 2.5 mmol), and the mixture was stirred for 18 hours. The mixture was concentrated to give a residue, which was dissolved in water (10 ml) and

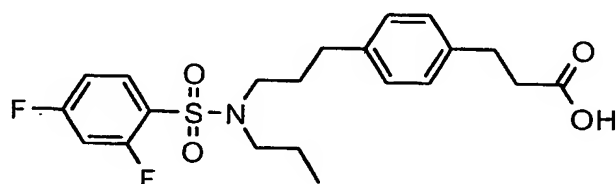
25

ethyl acetate (15 ml), and then the mixture was adjusted to pH 3 with 5N HCl. After extracting the aqueous layer with ethyl acetate (10 ml), the combined organic extracts were washed with water (15 ml) and brine (20 ml), dried (Na_2SO_4) and concentrated to provide about 25 mg of the title compound as an oil.

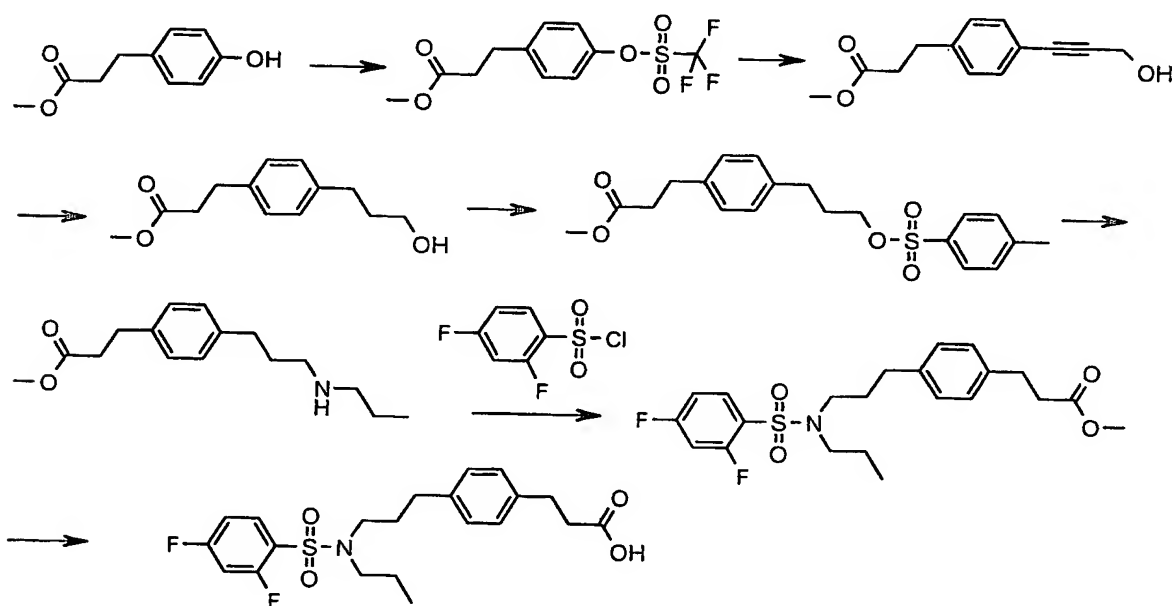
5

Example 387

3-(4-{3-[(2,4-Difluorobenzenesulfonyl)propylamino]propyl}phenyl) propionic acid



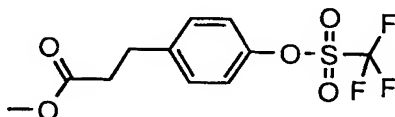
The compound of 3-(4-{3-[(2,4-difluorobenzenesulfonyl)propylamino]-
10 propyl}phenyl) propionic acid was prepared according to the scheme provided below:



-360-

Step A

3-(4-Trifluoromethanesulfonyloxyphenyl)propionic acid methyl ester

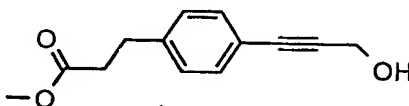


To a 500 mL round bottom flask under a nitrogen atmosphere were
 5 charged with methyl 3-(4-hydroxyphenyl)propionate (10.0g, 55.5 mmol) and phenyl N-phenyltriflimide (20.4 g, 57.2 mmol) dissolved in 150 mL anhydrous MeCl₂ (JOC, 55, 906-910, 1990). The stirred solution was cooled to 0 °C for 1 h and triethylamine was added dropwise (8.3 mL, 59.9 mmol). The reaction was allowed to warm up to ambient temperature and diluted with 500 mL ether, which was washed with water and brine, and
 10 then dried over Na₂SO₄ and concentrated. The crude material was purified by medium pressure HPLC normal phase silica gel chromatography utilizing a Biotage 65M cartridge eluting with 10:90 EtOAc:Hex to give a colorless oil (13.4 g, 77%). ¹H NMR (400 MHz, CDCl₃) δ 2.64 (t, J= 7.6 Hz, 2H), 2.98 (t, J= 7.6 Hz, 2H), 3.67 (s, 3H), 7.19 (d, J= 8.8 Hz, 2H), 7.28 (d, J= 8.8 Hz, 2H), MS (ES) *m/e* 330 (M+NH₄).

15

Step B

3-[4-(3-Hydroxyprop-1-ynyl)phenyl]propionic acid methyl ester



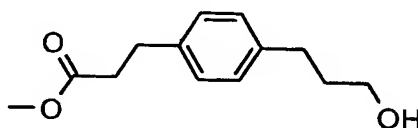
To a flame-dried 50 mL round bottom flask under an argon atmosphere were charged with 3-(4-trifluoromethanesulfonyloxyphenyl)propionic acid methyl ester
 20 (1.0 g (3.20 mmol), and propargyl alcohol (1.12 mL, 19.2 mmol) dissolved in anhydrous DMF, followed by the addition of triethylamine (1.78 mL, 12.8 mmol) and dichloridobis(triphenylphosphine)- palladium (II) (0.112 g 0.16 mmol) (Heterocycles, 38, 2463-2472, 1994). The mixture was heated to 90 °C for 2 h. The mixture was concentrated, diluted with 200 mL EtOAc, washed with brine, dried over Na₂SO₄, and
 25 concentrated. The crude residue was purified using radial chromatography (25:75 to 35:65 EtOAc:Hex) to give a yellow oil (0.29 g, 42%). ¹H NMR (400 MHz, CDCl₃) δ 1.64 (t, J= 6.1 Hz, 1H), 2.62 (t, J= 7.8 Hz, 2H), 2.94 (t, J= 7.8 Hz, 2H), 3.67 (s, 3H), 4.49

-361-

(d, $J = 5.9$ Hz, 2H), 7.15 (d, $J = 8.3$ Hz, 2H), 7.36 (d, $J = 8.3$ Hz, 2H). MS (ES) m/e 219 (M+1).

Step C

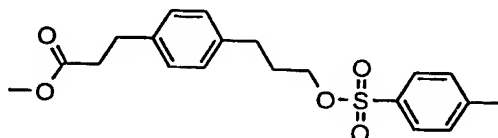
3-[4-(3-Hydroxypropyl)phenyl]propionic acid methyl ester



To a 100 mL round bottom flask was charged with 3-[4-(3-hydroxyprop-1-ynyl)phenyl] propionic acid methyl ester (1.0 g, 4.58 mmol) dissolved in 20 mL of THF. Pd/C (10%) was added and the reaction mixture was stirred under a balloon containing hydrogen for 16 h. The catalyst was filtered through celite, and the filtrate was concentrated to give a white solid (0.97 g, 97%). ^1H NMR (400 MHz, CDCl_3) δ 1.25 (br s, 1H), 1.85-1.92 (m, 2H), 2.60-2.70 (m, 4H), 2.92 (t, $J = 7.8$ Hz, 2H), 3.67 (s, 5H), 7.12 (s, 4H). MS (ES) m/e 223 (M+1).

Step D

3-{4-[3-(Toluene-4-sulfonyloxy)propyl]phenyl}propionic acid methyl ester



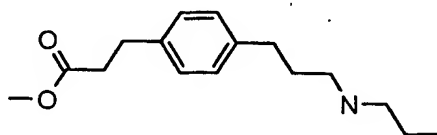
To a 250 mL round bottom flask was charged with 3-[4-(3-hydroxypropyl)phenyl]- propionic acid methyl ester (1.42 g, 6.39 mmol) dissolved in 25 mL of anhydrous MeCl_2 , followed by the addition of 4-dimethylaminopyridine (0.23 g, 1.92 mmol) and pyridine (1.76 mL, 21.7 mmol). The compound of *p*-toluenesulfonic anhydride (2.50 g, 7.67 mmol) was added. The reaction mixture was stirred at ambient temperature for 16 h and treated with 25 mL 1N HCl and stirred vigorously for 1 h. The layers were separated and the MeCl_2 was washed with brine, dried over Na_2SO_4 and concentrated. The crude material was purified by medium pressure HPLC normal phase silica gel chromatography utilizing a Biotage 40L cartridge eluting with 15:85 EtOAc:Hex to give a yellow oil (1.95 g, 81%). ^1H NMR (400 MHz, CDCl_3) δ 1.90-1.97 (m, 2H), 2.46 (s, 3H), 2.58-2.63 (m, 4H), 2.90 (t, $J = 7.8$ Hz, 2H), 3.67 (s, 3H), 4.02 (t, $J =$

-362-

6.4 Hz, 2H), 6.99 (d, $J = 7.8$ Hz, 2H), 7.07 (d, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.80 (d, $J = 8.3$ Hz, 2H). MS (ES) m/e 377 ($M+1$).

Step E

3-[4-(3-Propylaminopropyl)phenyl]propionic acid methyl ester



To a 250 mL round bottom flask was charged 3-{4-[3-(toluene-4-sulfonyloxy) propyl]phenyl}propionic acid methyl ester (1.82 g, 4.83 mmol) dissolved in 54 mL of anhydrous DMF, followed by the slow addition of *n*-propylamine (1.99 mL 24.17 mmol). The reaction mixture was stirred at ambient temperature for 18 h and then poured into 100 mL EtOAc and 50 mL water. The aqueous layer was washed with fresh EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated to give a thin yellow oil (1.3 g. quantitative). ^1H NMR (400 MHz, CDCl_3) δ 0.91 (t, $J = 7.6$ Hz, 3H), 1.85 (q, $J = 7.8$ Hz, 2H), 2.19 (q, $J = 7.7$ Hz, 2H), 2.57-2.65 (m, 4H), 2.78-2.91 (m, 6H), 3.67 (s, 3H), 7.09 (s, 4H), 9.40 (br s, 1H). MS (ES) m/e 264 ($M+1$).

Step F

3-(4-{3-[(2,4-Difluorobenzenesulfonyl)propylamino]propyl}phenyl)propionic acid

To a 1 dram screw capped vial were charged with 3-[4-(3-propylaminopropyl) phenyl] propionic acid methyl ester (0.092 g, 0.30 mmol), triethylamine (0.42 mL, 3.0 mmol), and 2,4-difluorobenzenesulfonyl chloride (0.096 g, 0.17 mmol) in 1 mL anhydrous MeCl_2 . The mixture was shaken at ambient temperature for 18 h. Next *N,N*-dimethylethylamine was added (0.033 mL, 0.30 mmol) and the vial was shaken for 1 h. After diluting with 1 mL MeOH, the reaction was poured into a 5 g SCX cartridge and eluted with 1:1 MeCl_2 :MeOH. The solvent was removed under a stream of nitrogen, and the residue was transferred to a 50 mL DynaVac carousel glass tube with screw cap. The residue was dissolved in 1 mL EtOH, treated with 0.3 mL 5N NaOH, and heated to 55 °C for 2 h. After removing the solvent under a stream of nitrogen, the residue was diluted with 1 mL MeCl_2 and 0.5 mL 5N HCl and poured into a Varian ChemElut 1003 cartridge. The cartridge was eluted with MeCl_2 . The eluent was

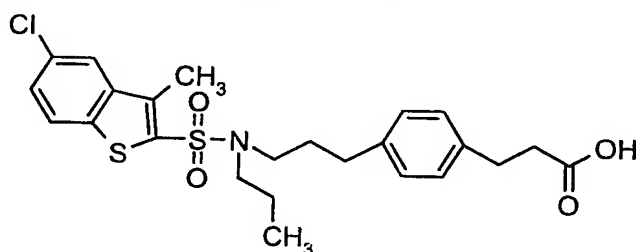
-363-

concentrated under a stream of nitrogen. The crude residue was purified by mass-directed reverse phase HPLC to provide 0.041 g (32%) of the acid compound. MS (ES) m/e 513 (M+1).

The following Examples 388 to 392 were prepared according to the procedure described above in Example 387.

Example 388

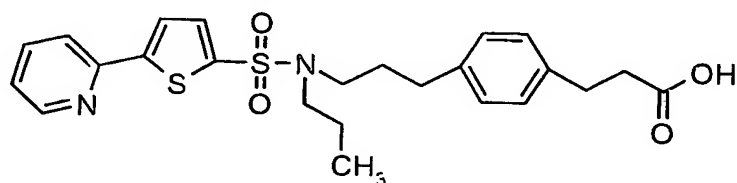
3-(4-{3-[(5-Chloro-3-methylbenzo[*b*]thiophene-2 sulfonyl)propylamino]propyl}phenyl)propionic acid



MS (ES) m/e 495 (M+1).

Example 389

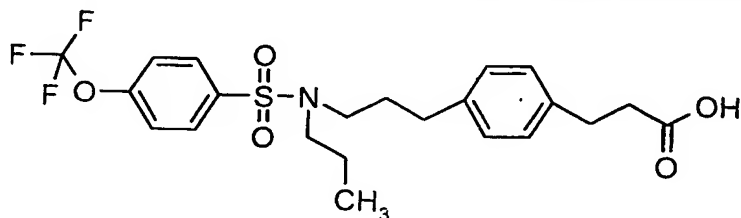
3-(4-{3-[Propyl(5-pyridin-2-ylthiophene-2-sulfonyl)amino]propyl}phenyl)propionic acid



MS (ES) m/e 473 (M+1).

Example 390

3-(4-{3-[Propyl(4-trifluoromethoxybenzenesulfonyl)amino]propyl}phenyl)propionic acid

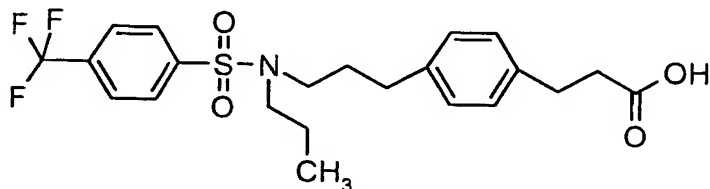


MS (ES) m/e 474 (M+1).

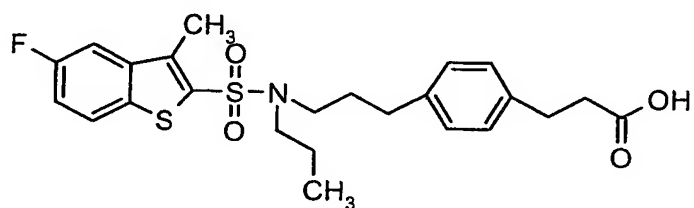
-364-

Example 391

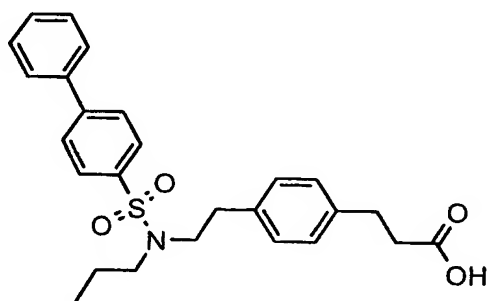
3-(4-{3-[Propyl(4-trifluoromethylbenzenesulfonyl)amino]propyl}phenyl)propionic acid

MS (ES) *m/e* 458 (M+1).

5

Example 3923-(4-{3-[(5-Fluoro-3-methylbenzo[*b*]thiophene-2-sulfonyl)propylamino]propyl}phenyl)propionic acid10 MS (ES) *m/e* 478 (M+1).Example 393

3-(4-{2-[(Biphenyl-4-sulfonyl)propylamino]ethyl}phenyl)propionic acid

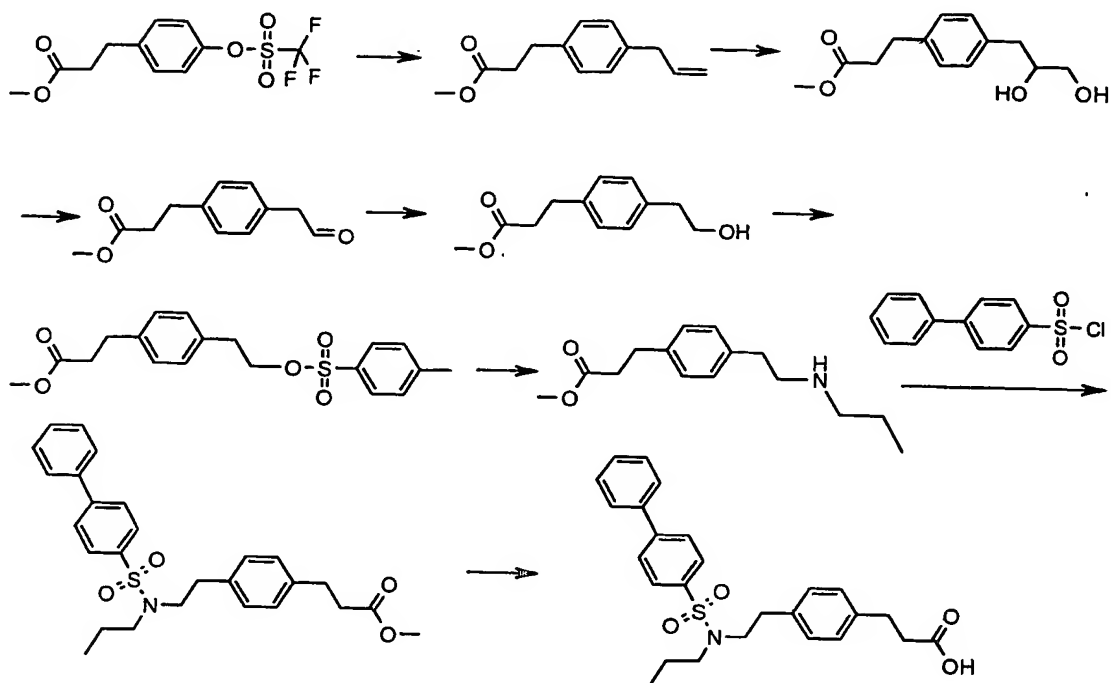


15

The compound of 3-(4-{2-[(biphenyl-4-sulfonyl)propylamino]ethyl}

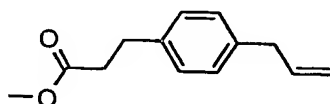
-365-

phenyl)propionic acid was prepared according to the scheme provided below:



Step A

3-(4-Allylphenyl)propionic acid methyl ester



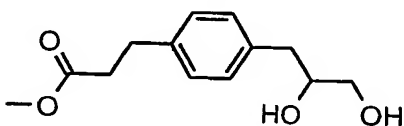
To a flame dried 250 mL round bottom flask under an argon atmosphere in 50 mL of anhydrous DMF were charged with 3-(4-trifluoromethanesulfonyloxyphenyl)-propionic acid methyl ester (2.0 g, 6.40 mmol), lithium chloride (2.28 g, 53.8 mmol), triphenylphosphine (1.01 g, 3.84 mmol), dichlorobis(triphenylphosphine)palladium (II) (0.54 g, 0.77 mmol) and then allyltributyltin (3.97 mL, 12.8 mmol) (JOC, 57, 678-685, 1992). The reaction was heated to 95°C for 2.5 h. The solvent was concentrated, and the residue was dissolved in 300 mL EtOAc and washed with 200 mL 2N HCl (4x), 100 mL 5% KF (1x), brine, dried over Na₂SO₄ and concentrated. The crude material was purified by medium pressure HPLC normal phase silica gel chromatography using a Biotage 65M cartridge eluting with 5:95 EtOAc:Hex. This oil was treated further with a saturated KF/ether trituration followed by an EtOAc extraction. The organic layer was washed

-366-

with brine, dried over Na_2SO_4 , and concentrated to give a colorless oil (0.56 g, 42%). MS (ES) m/e 205 ($M+1$).

Step B

3-[4-(2,3-Dihydroxypropyl)phenyl]propionic acid methyl ester



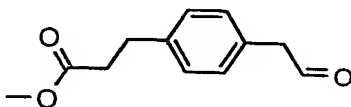
5

To a 250 mL round bottom flask was charged with 3-(4-allylphenyl)propionic acid methyl ester (10.2 g, 49.9 mmol) dissolved in 100 mL acetone followed by the addition of 4-methylmorpholine *N*-oxide (8.1 g, 59.9 mmol) and water (10 mL). Osmium tetroxide (3 chips) was added and the reaction was stirred at ambient temperature for 4 h. The reaction was poured into 500 mL EtOAc and washed twice with $\text{Na}_2\text{S}_2\text{O}_3$, brine, dried over Na_2SO_4 and concentrated to give a soft off-white solid (9.75 g, 81%). MS (ES) m/e 256 ($M+\text{NH}_4$).

10

Step C

3-[4-(2-Oxoethyl)phenyl]propionic acid methyl ester



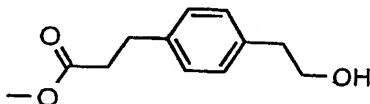
15

To a 100 mL round bottom flask was charged 3-[4-(2,3-dihydroxypropyl)phenyl]propionic acid methyl ester (0.82 g, 2.45 mmol) dissolved in 12 mL each of THF and water. Sodium periodate (1.57 g, 7.35 mmol) was added, and the reaction was stirred at ambient temperature for 2 h. The reaction was poured into 50 mL EtOAc and 25 mL brine. The organic layer was washed with $\text{Na}_2\text{S}_2\text{O}_3$ solution, brine, dried over Na_2SO_4 and concentrated to give a colorless oil (0.42 g, 83%). MS (ES) m/e 207 ($M+1$).

20

Step D

3-[4-(2-Hydroxyethyl)phenyl]propionic acid methyl ester



25

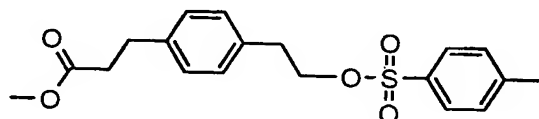
To a 250 mL round bottom flask was charged with 3-[4-(2-oxoethyl)phenyl] propionic acid methyl ester (2.11 g, 10.2 mmol) dissolved in 35 mL

-367-

anhydrous THF and 25 mL anhydrous MeOH. The solution was cooled down in an ice bath followed by the portion-wise addition of sodium borohydride (0.58 g, 15.3 mmol). The cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 2 h. The mixture was poured into 200 mL EtOAc and 100 mL ice water, and then 1N HCl (50 mL) was added slowly. The aqueous layer was discarded, and the organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The crude residue was purified using radial chromatography (2:98 to 5:95 MeOH:MeCl₂) to give a white solid (0.89 g, 42%). MS (ES) *m/e* 226 (M+NH₄).

Step E

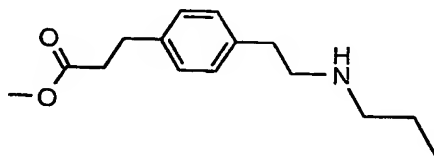
3-{4-[2-(Toluene-4-sulfonyloxy)ethyl]phenyl}propionic acid methyl ester



To a 100 round bottom flask was charged with 3-[4-(2-hydroxyethyl)phenyl] propionic acid methyl ester (0.89 g, 4.27 mmol) dissolved in 16 mL of anhydrous MeCl₂, followed by the addition of 4-dimethylaminopyridine (0.156 g, 1.28 mmol) and pyridine (1.17 mL, 14.5 mmol). The compound of *p*-toluenesulfonic anhydride (1.67 g, 5.13 mmol) was added, and the reaction was stirred at ambient temperature for 16 h. The reaction was treated with 15 mL 1N HCl and stirred vigorously for 1 h. The layers were separated, and the MeCl₂ was washed with brine, dried over Na₂SO₄ and concentrated. The crude residue was purified using radial chromatography (5:95 to 25:75 EtOAc:Hex) to give a yellow oil (1.3 g, 84%). MS (ES) *m/e* 380 (M+NH₄).

Step F

3-[4-(2-Propylaminoethyl)phenyl]propionic acid methyl ester



To a 250 mL round bottom flask was charged 3-{4-[2-(toluene-4-sulfonyloxy)ethyl]phenyl}propionic acid methyl ester (1.28 g, 3.53 mmol) dissolved in 40 mL of anhydrous DMF, followed by the slow addition of *n*-propylamine (1.45 mL, 17.66

-368-

mmol). The reaction was stirred at ambient temperature for 30 h and poured into 100 mL EtOAc and 50 mL water. The aqueous layer was washed with fresh EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated to give a yellow oil (0.88 g, quantitative). MS (ES) *m/e* 250 (M+1).

5

Step G

3-(4-{2-[(Biphenyl-4-sulfonyl)propylamino]ethyl}phenyl)propionic acid

A 50 mL glass tube with screw cap and nitrogen inlet was charged with sequentially with 3-[4-(3-propylaminopropyl)phenyl]propionic acid methyl ester (0.10 g, 0.40 mmol), anhydrous MeCl₂ (1.5 mL), triethylamine (0.17 mL, 1.2 mmol), and 4-biphenylsulfonyl chloride (0.152 g, 0.60 mmol). The mixture was stirred at ambient temperature for 18 h and concentrated under a stream of N₂. The residue was dissolved in EtOH (1.5 mL), treated with 2N NaOH (0.40 mL, 2.0 mmol), and heated at 55 °C for 3 h. The mixture was concentrated under a stream of N₂. The residue was treated with MeCl₂ (2 mL), water (0.5 mL), and 5N HCl (0.64 mL, 3.2 mmol). The mixture was poured into a Varian ChemElut 1003 drying cartridge and was eluted with MeCl₂. The crude residue was purified by mass-directed reverse phase HPLC to provide 0.12 g (68%) of the final acid compound. MS (ES) *m/e* 513 (M+1).

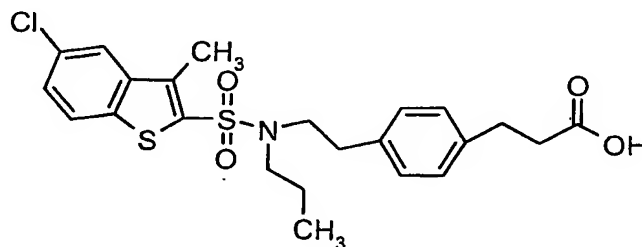
15

The following Examples 394 and 395 were prepared according to the procedure described above in Example 393.

20

Example 394

3-(4-{2-[(5-Chloro-3-methylbenzo[*b*]thiophene-2-sulfonyl)propylamino]ethyl}phenyl)propionic acid

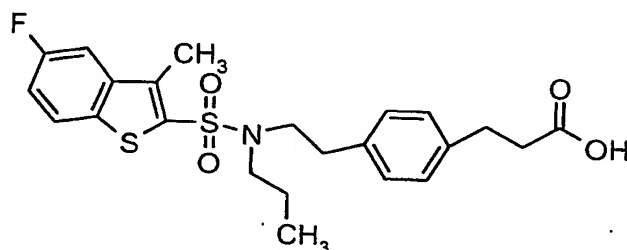


25 MS (ES) *m/e* 481 (M+1).

-369-

Example 395

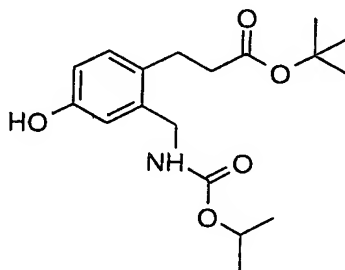
3-(4-{2-[(5-Fluoro-3-methylbenzo[*b*]thiophene-2-sulfonyl)propylaminoethyl}phenyl)propionic acid



5 MS (ES) *m/e* 464 (M+1).

Example 396

3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester



10

Slurry of 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (75.4 g, 0.3 mol) in CH₂Cl₂ (900 mL) at 1°C was treated with triethylamine (60.7 g, 0.6 mol). Isopropyl chloroformate (300 mL, 0.3 mol, 1M in toluene) was added while maintaining the temperature less than 12°C. The resulting solution was stirred 16 h at ambient temperature. After 16 h, additional isopropyl chloroformate (15 mL, 0.015 mol, 1.0M in toluene) was added, and the reaction was stirred for 1 h. The reaction mixture was washed with 1N HCl (2 x 200 mL) and saturated NaHCO₃ solution (2 x 200 mL). The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by filtration through Merck silica gel 62 (750 grams, CH₂Cl₂/MeOH 100/0 to 96/4) to give the title compound (95.48 g, 94.3%). ¹H NMR (300 MHz, CDCl₃): δ 1.20-1.24 (d, 6H), 1.40 (s, 9H), 2.46-2.52 (t, 2H), 2.81-2.86 (t, 2H), 4.29-4.32 (d, 2H), 4.86-4.97 (m, 1H), 4.97-5.08 (m, 1H), 6.67-6.72 (dd, 2H), 6.76 (s, 1H), 6.97-7.00 (d, 1H). MS (ES⁺) *m/z* 336.1 [M-H]⁺.

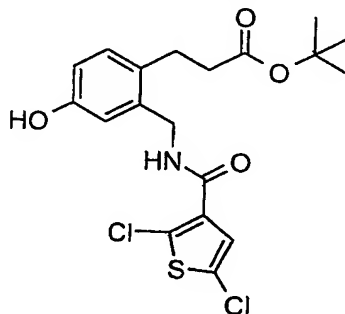
15

20

-370-

Example 397

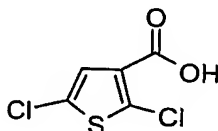
3-(2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-hydroxy-phenyl)-propionic acid tert-butyl ester



5

Step A

2,5-Dichloro-thiophene-3-carboxylic acid



A mixture of the 1-(2,5-dichloro-thiophen-3-yl)-ethanone (10 g, 51.26 mmol) and 9.5% NaOCl (150 mL, 230 mmol, 4.5 eq., commercial bleach) was treated with 5N NaOH (1 mL, 5 mmol, 0.1 eq.). The mixture was stirred vigorously and heated to 55 °C. The internal temperature was monitored closely and heat was removed to control the exotherm. After 6 h at 61 °C, starting material was completely consumed. The mixture was cooled to 0 °C and carefully quenched with 20 % aq. NaHSO₃ solution (20 mL). At 0 °C, 6M HCl (12 mL) was added to adjust the pH to 1.5. The mixture was extracted with EtOAc (300 mL and 3 x 50 mL). The combined organic layers were washed with brine (200 mL), dried (Na₂SO₄), and concentrated to a white solid (8.8 g).

Step B

3-(2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-hydroxy-phenyl)-propionic acid tert-butyl ester

20

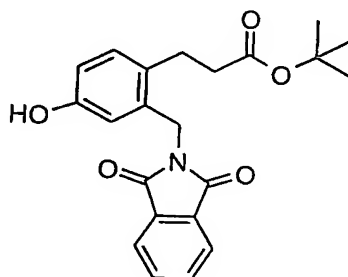
A solution of the 2,5-dichloro-thiophene-3-carboxylic acid (12.9g, 65.5 mmol) and 4-methylmorpholine (7.17 mL, 65.2 mmol) in dry THF (400 mL) was cooled to -15 °C. Isobutyl chloroformate (8.46 mL, 65.2 mmol) was added. The mixture was stirred 3 min and triethylamine (9.1 mL, 65 mmol) was added. A solution of 3-(2-aminomethyl-4-hydroxy-phenyl)-propionic acid tert-butyl ester (16.4 g, 65.3 mmol) in

-371-

DMF (130 mL) pre-cooled to -15°C was added via cannula over 15 min. After stirring 1 h, TLC indicated complete reaction. The reaction mixture was allowed to warm to ambient temperature. Solids were removed by filtration and washed with THF (100 mL). The filtrate was diluted with Et_2O (500 mL) and washed with water (250 mL) then brine (150 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude brown oil was purified by silica gel chromatography (hexanes/ EtOAc 2/1) and recrystallization (toluene) to afford the title compound as a white crystalline solid (22.3 g, 79.6%). MS (ES^+) m/z 430.1 $[\text{M}+\text{H}]^+$.

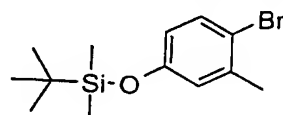
Example 398

3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-propionic acid tert-butyl ester



Step A

(4-Bromo-3-methyl-phenoxy)-tert-butyl-dimethyl-silane

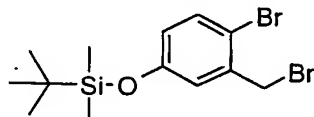


A 12 L flask was charged with 4-bromo-3-methyl phenol (428 g, 2.29 mol), CH_2Cl_2 (7.5 L), triethylamine (480 mL, 3.45 mol), and tert-butyldimethylsilyl chloride (324 g, 2.15 mol). To the solution was added 4-dimethylaminopyridine (15.0 g, 0.123 mol). The reaction mixture was stirred at ambient temperature overnight. The reaction was washed with saturated ammonium chloride (2.2 L) and then DI water (0.9 L). The organic layer was dried (Na_2SO_4), filtered, and concentrated to crude product (699 g). This material was purified by silica gel chromatography (heptane) to give the title compound (637 g, 98.5%).

-372-

Step B

(4-Bromo-3-bromomethyl-phenoxy)-tert-butyl-dimethyl-silane

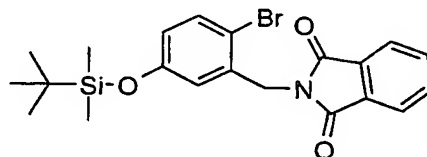


5 The compounds of (4-bromo-3-methyl-phenoxy)-tert-butyl-dimethyl-silane (255 g, 0.846 mol), dichloroethane (2.5 L), N-bromosuccinimide (165 g, 0.927 mol) and 2,2'-azobisisobutyronitrile (19.0 g, 0.116 mol) were combined in a 5 L flask. The mixture was degassed by evacuating and purging with N₂ (5x). The reaction mixture was heated to 47°C, and the heat was shut off. An exotherm to 76°C occurred. GC analysis showed 6.5% unreacted starting material. The heat was applied again, and the
10 reaction was held at reflux (83°C) for 15 min. After cooling to 8°C, heptane (1.0 L) was added. The resulting slurry was stirred at 4 °C for 30 min and filtered. The filtrate was evaporated to dryness. The residue was treated with heptane (1 L), placed in the freezer overnight, and filtered. The filtrate was concentrated to the title compound (326 g, 101%).

15

Step C

2-[2-Bromo-5-(tert-butyl-dimethyl-silanyloxy)-benzyl]-isoindole-1,3-dione

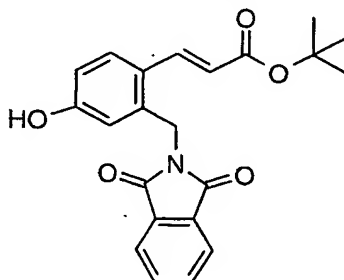


A 12 L flask was charged with (4-bromo-3-bromomethyl-phenoxy)-tert-butyl-dimethyl-silane (568 g 1.49 mol), DMF (3.1 L), and potassium phthalimide (316 g 1.71 mol). An exotherm to 34 °C occurred. After 40 min, the reaction mixture was cooled to 18°C. Ether (6.2 L) and DI water (4.9 L) were added, and the layers were separated. The organic layer was washed with saturated NaCl solution (2 L), dried (Na₂SO₄), filtered, and concentrated. The residue was recrystallized from heptane (1.5 L) to give the title compound (454 g, 68%).
20

-373-

Step D

3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-acrylic acid tert-butyl ester



5 A 12 L flask was charged with 2-[2-bromo-5-(tert-butyl-dimethyl-
silanyloxy)-benzyl]-isoindole-1,3-dione (461 g, 1.03 mol), propionitrile (7 L), tri-*ortho*-
tolyl phosphine (76.0 g, 0.250 mol) and diisopropyl ethyl amine (365 mL, 2.10 mol). The
reaction mixture was degassed/purged with N₂ (3x), and tert-butyl acrylate (465 mL, 3.17
mol) was added. After degassing/purging one time, palladium (II) acetate (28.0 g, 0.125
10 mol) was added. The stirred mixture was degassed/purged with N₂ three times and heated
to 95°C for 20 h. The mixture was filtered through a hyflo cake, washed with
acetonitrile, and concentrated to a brown oil (841 g). The residue was dissolved in THF
(3.5 L), and tetrabutylammonium fluoride (TBAF, 650 mL, 0.65 mol, 1M in THF) was
added. After 1 h, additional TBAF (95 mL) was added. The mixture was rotated on the
15 rotary evaporator for 10 min and was concentrated to crude product (987 g). This
material was purified by silica gel chromatography (toluene/ethyl acetate, 100/0 to 75/25)
to give the title compound (340 g, 86.8%).

Step E

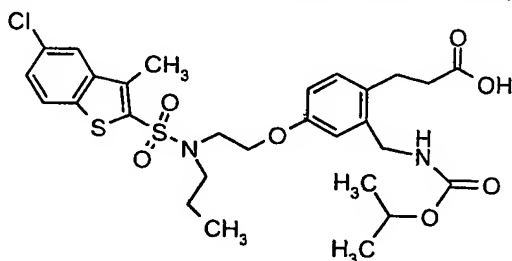
20 3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-propionic acid tert-butyl ester

A 1 gallon autoclave was charged with 3-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxy-phenyl]-acrylic acid tert-butyl ester (196 g, 0.517 mol), ethyl acetate (2.6 L) and 5 % palladium on carbon (75 g). The autoclave was kept at 25°C under 60 psi of hydrogen for 21 h. The temperature of the reaction was increased to 40 °C. and the pressure was increased to 75 psi for 5 h. The mixture was filtered through a pad of hyflo and concentrated to the title compound (186 g, 94.4 %). MS (ESI) m/z 380.2 (M-H)⁻.

-374-

Example 399

3-[4-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid



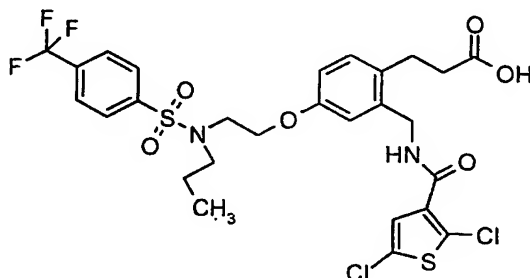
5 A mixture of 3-[4-hydroxy-2-(isopropoxycarbonylamino-methyl)-phenyl]-propionic acid tert-butyl ester (34 mg, 0.10 mmol) (see Example 396), toluene-4-sulfonic acid 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethyl ester (55 mg, 0.110 mmol), and potassium carbonate (100 mg, 0.725 mmol, 100 mesh) in DMF (1 mL) was heated to 65 °C for 18 h. The mixture was quenched with water (15 mL) and
 10 extracted with EtOAc (2 x 15 mL). The organic layer was dried (Na₂SO₄) and concentrated. The crude product was purified by silica gel chromatography (20-40% EtOAc/Hex). The ester was dissolved in CH₂Cl₂ (1 mL), treated with TFA (0.3 mL) and water (0.05 mL), and stirred at ambient temperature for 2 h. The solution was concentrated to give the title compound. MS (ESI) m/z 611.2 (M+H)⁺.

15 The following Examples 400 to 404 were prepared according to the procedure described above in Example 399 by using an appropriate headpiece as described in Examples 396 to 398.

-375-

Example 400

3-(2-{[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-{2-[propyl-(4-trifluoromethyl)-benzenesulfonyl]-amino]-ethoxy}-phenyl)-propionic acid



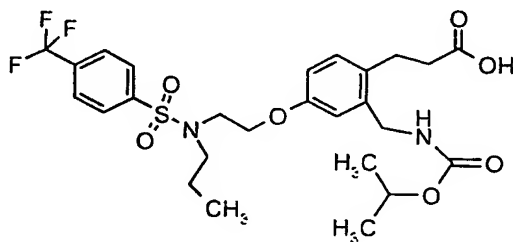
5

^1H NMR (400 MHz, CDCl_3) δ 0.78 (t, $J = 7.3$ Hz, 3H), 1.51-1.56 (m, 2H), 2.60 (t, $J = 7.6$ Hz, 2H), 2.89 (t, $J = 7.3$ Hz, 2H), 3.13 (apparent t, $J = 7.6$ Hz, 2H), 3.44 (t, $J = 5.9$ Hz, 2H), 4.01 (t, $J = 6.1$ Hz, 2H), 4.52 (d, $J = 5.4$ Hz, 2H), 6.60 (dd, $J = 2.6, 8.1$ Hz, 1H), 6.70-6.74 (m, 1H), 6.73 (d, $J = 2.9$ Hz, 1H), 7.03 (d, $J = 8.3$ Hz, 1H), 7.12 (s, 1H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.85 (d, $J = 8.3$ Hz, 2H).

10

Example 401

3-(2-(Isopropoxycarbonylamino-methyl)-4-{2-[propyl-(4-trifluoromethyl)-benzenesulfonyl]-amino]-ethoxy}-phenyl)-propionic acid



15

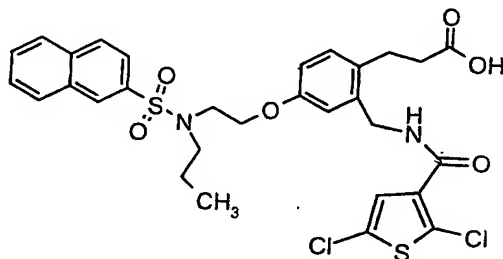
MS (ESI) m/z 575.3 ($\text{M}+\text{H}$) $^+$.

20

-376-

Example 402

3-(2-{[(2,5-Dichloro-thiophene-3-carbonyl)-amino]-methyl}-4-{2-[(naphthalene-2-sulfonyl)-propyl-amino]-ethoxy}-phenyl)-propionic acid

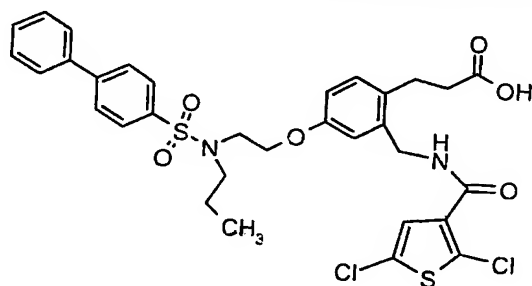


5

MS (ESI) m/z 649.1 (M+H)⁺.

Example 403

3-(4-{2-[(Biphenyl-4-sulfonyl)-propyl-amino]-ethoxy}-2-{[(2,5-dichloro-thiophene-3-carbonyl)-amino]-methyl}-phenyl)-propionic acid



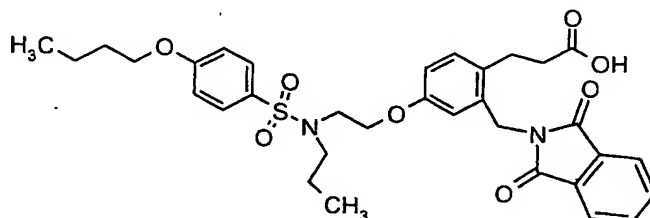
MS (ESI) m/z 675.2 (M+H)⁺.

15

-377-

Example 404

3-[4-{2-[(4-Butoxy-benzenesulfonyl)-propyl-amino]-ethoxy}-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-phenyl]-propionic acid

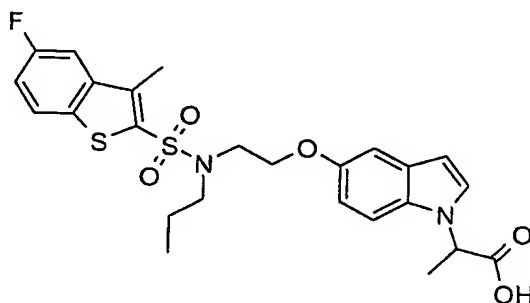


5

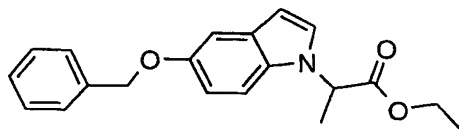
MS (ESI) m/z 623.2 ($M+H$)⁺.

Example 405

2-(5-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-indol-1-yl)-propionic acid

Step A

2-(5-Benzyloxy-indol-1-yl)-propionic acid ethyl ester



15

NaH (60% w/w suspension in mineral oil, 5.37g, 134mmol) was added portion wise to a chilled (0°C) solution of 5-benzyloxy-indole (25.0g, 112mmol) in DMF (125mL). The mixture was stirred at 0°C under N₂ for 30min, and then warmed to room temperature. Ethyl 2-bromo-propionate (16.5mL, 20.0g, 123mmol – exotherm to 50°C) was added and the mixture was heated to 70°C overnight. The mixture was cooled to 0°C and NaH (2.5g, 62.5mmol) and DMF (90mL) were added. The mixture was warmed to room temperature for 30min, and ethyl 2-bromo-propionate (8mL, 11.2g, 60mmol) was

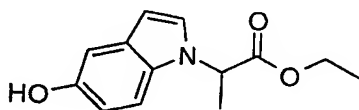
20

-378-

added. The mixture was heated to 70°C overnight, cooled to room temperature, and diluted with ethyl acetate (300mL). Organics were washed twice with 1.00N HCl (200mL), dried (MgSO₄), filtered, and concentrated. Crude material was purified by silica gel chromatography (800g) eluting with 92:8 hexanes:EtOAc to afford 10.2g (28%) of the title compound as a pink oil. ¹H-NMR (CDCl₃) δ 1.25 (t, 3H), 1.83 (d, 3H), 4.20 (q, 2H), 5.09 (q, 1H), 5.15 (s, 2H), 6.52 (d, 1H), 7.00 (dd, 1H), 7.20 (d, 1H), 7.27 (d, 2H), 7.33-7.46 (m, 3H), 7.51 (dd, 2H); MS [ES] 324 (M+H).

Step B

2-(5-Hydroxy-indol-1-yl)-propionic acid ethyl ester



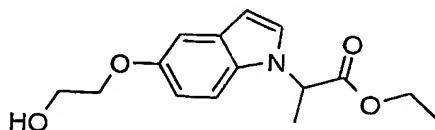
10

To a solution of 2-(5-benzyloxy-indol-1-yl)-propionic acid ethyl ester (7.0g, 21mmol) in EtOH (90mL) was added 5%Pd/C (875mg). The resulting mixture was shaken for 6h at room temperature under H₂ (60psi). which was then filtered and concentrated to afford 4.0g (87%) of the title compound as a tan oil. ¹H-NMR (CDCl₃) δ 1.12 (t, 3H), 1.71 (d, 3H), 4.08 (q, 2H), 4.97 (q, 1H), 6.35 (d, 1H), 6.69 (dd, 1H), 6.94 (d, 1H), 7.08 (d, 1H), 7.16 (d, 1H); MS [ES] 234 (M+H).

15

Step C

2-[5-(2-Hydroxy-ethoxy)-indol-1-yl]-propionic acid ethyl ester



20

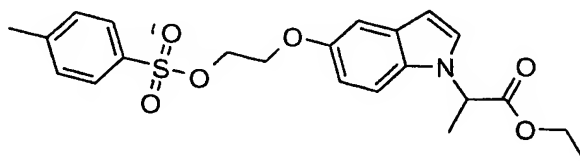
A mixture of 2-(5-hydroxy-indol-1-yl)-propionic acid ethyl ester (3.75g, 16.1mmol), ethylene carbonate (7.08g, 80.4mmol), DABCO (270mg, 2.41mmol), Na₂SO₄ (2g, 14mmol), and tert-butanol (30mL) was heated to reflux for 45min and stirred at room temperature overnight. The mixture was concentrated *in-vacuo*, and diluted with 1.00N HCl and water, which was then extracted into ethyl acetate, dried (MgSO₄), filtered, and concentrated. The resulting material was purified on silica gel (600g) by eluting with 80:20 hexanes:EtOAc to afford 3.16g (71%) of the title compound as a yellow oil. MS [ES] 278 (M+H).

25

-379-

Step D

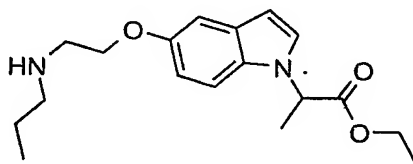
2-{5-[2-(Toluene-4-sulfonyloxy)-ethoxy]-indol-1-yl}-propionic acid ethyl ester



Standard Procedure (I), which described in Example 261 was utilized with
 5 2-[5-(2-hydroxy-ethoxy)-indol-1-yl]-propionic acid ethyl ester to afford the title
 compound as a colorless oil. ¹H-NMR (CDCl₃) δ 1.23 (t, 3H), 1.83 (d, 3H), 2.48 (s, 3H),
 4.19 (m, 4H), 4.42 (t, 2H), 5.08 (q, 1H), 6.48 (d, 1H), 6.78 (dd, 1H), 7.00 (d, 1H), 7.21 (d,
 1H), 7.28 (d, 1H), 7.36 (d, 2H), 7.86 (d, 2H); MS [ES] 432 (M+H).

Step E

10 2-[5-(2-Propylamino-ethoxy)-indol-1-yl]-propionic acid ethyl ester



Standard Procedure (J) which described in Example 262 was utilized with
 2-{5-[2-(toluene-4-sulfonyloxy)-ethoxy]-indol-1-yl}-propionic acid ethyl ester to afford
 the title compound as a tan oil. ¹H-NMR (CDCl₃) δ 0.88 (t, 3H), 1.14 (t, 3H), 1.50 (m,
 15 2H), 1.73 (d, 3H), 2.20 (br s, 1H), 2.61 (t, 2H), 2.99 (t, 2H), 4.07 (m, 4H), 5.00 (q, 1H),
 6.41 (d, 1H), 6.80 (dd, 1H), 7.03 (d, 1H), 7.16 (m, 2H); MS [ES] 319 (M+H).

Step F

2-(5-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-
 indol-1-yl)-propionic acid

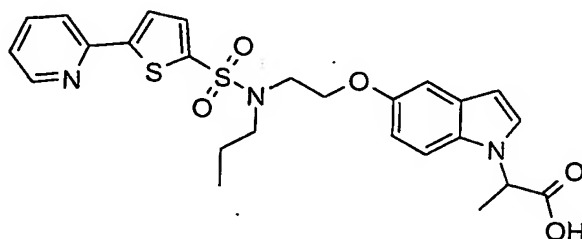
20 Standard Procedure (A) which described in Example 253 was utilized with
 2-[5-(2-propylamino-ethoxy)-indol-1-yl]-propionic acid ethyl ester and 5-fluoro-3-
 methyl-benzo[b]thiophene-2-sulfonyl chloride to prepare the title compound. ¹H-NMR;
 MS [ES] 519 (M+H), 517 (M-H).

The following Examples 406 and 407 were prepared according to the
 25 procedure described above in Example 405 by using the appropriate sulfonyl chlorides.

-380-

Example 406

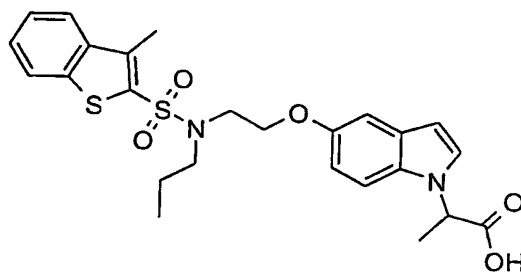
2-(5-{2-[Propyl-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-ethoxy}-indol-1-yl)-
propionic acid



5 ¹H-NMR: MS [ES] 514 (M+H), 512 (M-H).

Example 407

2-(5-{2-[(3-Methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-indol-1-yl)-
propionic acid



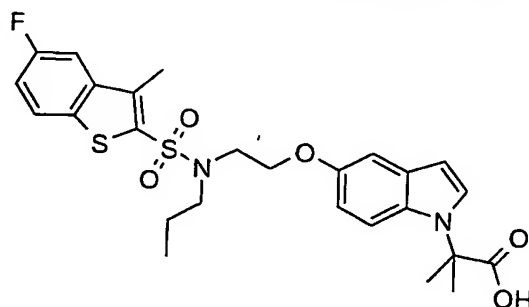
10

¹H-NMR: MS [ES] 501 (M+H), 499 (M-H).

Example 408

2-(5-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-
indol-1-yl)-2-methyl-propionic acid

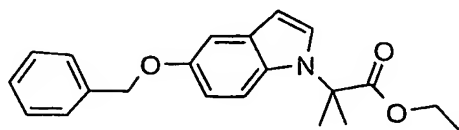
15



-381-

Step A

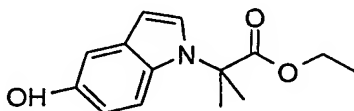
2-(5-Benzoyloxy-indol-1-yl)-2-methyl-propionic acid ethyl ester



LDA (2M in THF, 18.9mL, 37.9mmol) was added slowly (exothermic) to a chilled (-78°C) solution of 2-(5-benzoyloxy-indol-1-yl)-propionic acid ethyl ester (10.2g, 31.5mmol) in THF (90mL) under N₂. The reaction mixture was stirred for 30min under N₂ at -78°C, and CH₃I (3.93mL, 8.95g, 63.1mmol) was added. The mixture was warmed up to room temperature and concentrated *in-vacuo*. The residue was diluted with H₂O and extracted into EtOAc, which was then dried (MgSO₄), filtered, and concentrated. The material was purified by silica gel chromatography (300g) by eluting with 90:10 hexanes/EtOAc to afford 7.28g (68%) of the title compound as a yellow oil. ¹H-NMR (CDCl₃) δ 1.03 (t, 3H), 1.79 (s, 6H), 4.07 (q, 2H), 5.02 (s, 2H), 6.38 (d, 1H), 6.81 (dd, 1H), 7.02 (d, 1H), 7.09 (d, 1H), 7.16 (t, 1H), 7.22-7.35 (m, 3H), 7.40 (d, 2H); MS [ES] 338 (M+H).

Step B

2-(5-Hydroxy-indol-1-yl)-2-methyl-propionic acid ethyl ester

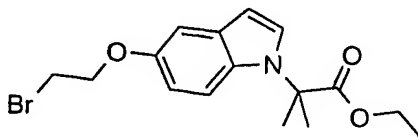


The procedure described in Example 405, Step B was used with 2-(5-benzoyloxy-indol-1-yl)-2-methyl-propionic acid ethyl ester to afford the title compound as a yellow oil. ¹H-NMR (CDCl₃) δ 1.04 (t, 3H), 1.78 (s, 6H), 4.07 (q, 2H), 4.69 (br s, 1H), 6.31 (d, 1H), 6.65 (dd, 1H), 6.95 (d, 1H), 7.17 (d, 1H), 7.19 (s, 1H); MS [ES] 248 (M+H).

-382-

Step C

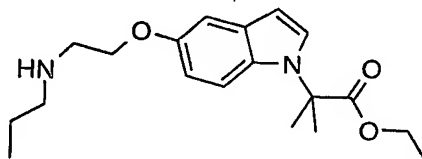
2-[5-(2-Bromo-ethoxy)-indol-1-yl]-2-methyl-propionic acid ethyl ester



Standard Procedure (H) which described in Example 260 was utilized with
 5 2-(5-hydroxy-indol-1-yl)-2-methyl-propionic acid ethyl ester to prepare the title compound as a colorless oil. ¹H-NMR (CDCl₃) δ 1.14 (t, 3H), 1.89 (s, 1H), 3.78 (t, 2H), 4.18 (q, 2H), 4.46 (t, 2H), 6.46 (d, 1H), 6.86 (dd, 1H), 7.13 (d, 1H), 7.29 (d, 1H), 7.30 (s, 1H); MS [ES] 354, 356 (M+H).

Step D

10 2-Methyl-2-[5-(2-propylamino-ethoxy)-indol-1-yl]-propionic acid ethyl ester



Standard Procedure (J) which described in Example 262 was utilized with
 2-[5-(2-bromo-ethoxy)-indol-1-yl]-2-methyl-propionic acid ethyl ester to prepare the title
 compound as a yellow oil. ¹H-NMR (CDCl₃) δ 0.87 (t, 3H), 1.03 (t, 3H), 1.52 (m, 2H),
 15 1.80 (s, 6H), 2.16 (br s, 1H), 2.64 (t, 2H), 2.98 (t, 2H), 4.06 (m, 4H), 6.36 (d, 1H), 6.74
 (dd, 1H), 7.00 (d, 1H), 7.13 (d, 1H), 7.18 (d, 1H); MS [ES] 333 (M+H).

Step E

2-(5-{2-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-
 indol-1-yl)-2-methyl-propionic acid

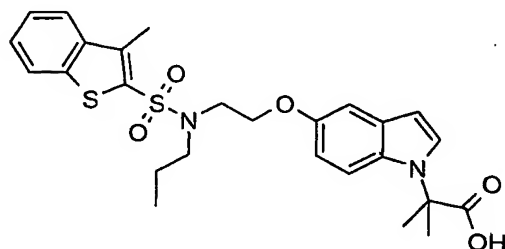
20 Standard Procedure (A) which described in Example 253 was utilized with
 2-methyl-2-[5-(2-propylamino-ethoxy)-indol-1-yl]-propionic acid ethyl ester and 5-
 fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride to prepare the title compound.
¹H-NMR: MS [ES] 533 (M+H), 531 (M-H).

25 The following Examples 409 to 411 were prepared according to the
 procedure described above in Example 408.

-383-

Example 409

2-Methyl-2-(5-{2-[(3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-indol-1-yl)-propionic acid



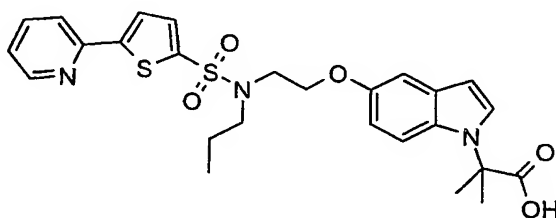
5

¹H-NMR; MS [ES] 515 (M+H), 513 (M-H).

Example 410

2-Methyl-2-(5-{2-[propyl-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-ethoxy}-indol-1-yl)-propionic acid

10

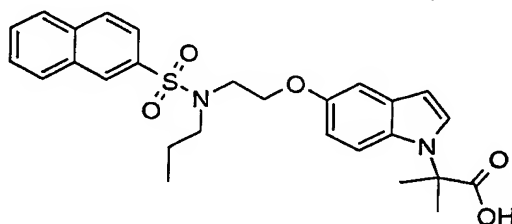


¹H-NMR; MS [ES] 528 (M+H), 526 (M-H).

15

Example 411

2-Methyl-2-(5-{2-[(naphthalene-2-sulfonyl)-propyl-amino]-ethoxy}-indol-1-yl)-propionic acid

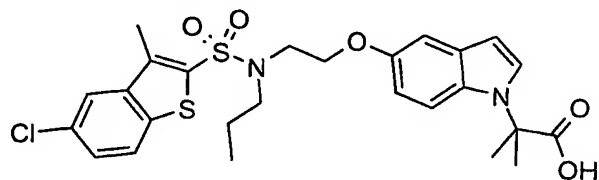


20 ¹H-NMR; MS [ES] 495 (M+H), 493 (M-H).

-384-

Example 412

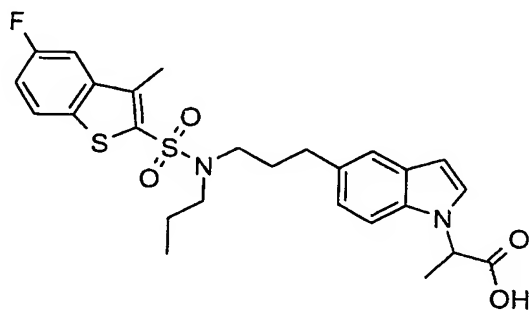
2-(5-{2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-ethoxy}-indol-1-yl)-2-methyl-propionic acid



5 The title compound was prepared by following the procedure described in Example 74, Step C by using 2-(5-hydroxy-indol-1-yl)-2-methyl-propionic acid ethyl ester to afford the compound as a white solid. ¹H-NMR (CDCl₃) δ 0.85 (t, 3H), 1.63 (m, 2H), 1.84 (s, 6H), 2.60 (s, 3H), 3.30 (m, 2H), 3.61 (t, 2H), 4.08 (t, 2H), 6.33 (d, 1H), 6.62 (dd, 1H), 6.89 (d, 1H), 7.03 (d, 1H), 7.19 (d, 1H), 7.36 (dd, 1H), 7.66 (m, 2H); MS [ES]
10 549 (M+H), 547 (M-H).

Example 413

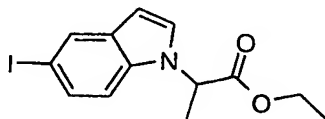
2-(5-{3-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-indol-1-yl)-propionic acid



15

Step A

2-(5-Iodo-indol-1-yl)-propionic acid ethyl ester

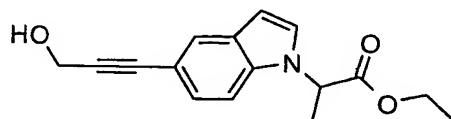


20 The title compound was prepared by following the procedure described in Example 387. Step A by using 5-iodoindole to prepare the title compound as a colorless oil. ¹H-NMR (CDCl₃) δ 1.23 (t, 3H), 1.84 (d, 3H), 4.19 (q, 2H), 5.10 (q, 1H), 6.52 (d, 1H), 7.12 (d, 1H), 7.26 (d, 1H), 7.47 (dd, 1H), 7.99 (d, 1H); MS [ES] 344 (M+H).

-385-

Step B

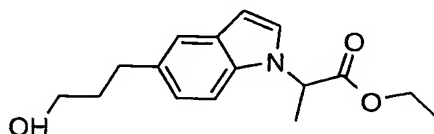
2-[5-(3-Hydroxy-prop-1-ynyl)-indol-1-yl]-propionic acid ethyl ester



Propargyl alcohol (6.11mL, 5.88g, 105mmol) in DMF (10mL) was added slowly to a mixture of 2-(5-iodo-indol-1-yl)-propionic acid ethyl ester (6.00g, 17.5mmol), Et₃N (9.75mL, 7.08g, 70.0mmol), and Pd(PPh₃)₂Cl₂ (614mg, 0.87mmol) in DMF (35mL). The mixture was stirred at room temperature under N₂ for 40h, and concentrated *in vacuo*, which was then diluted with 0.1N HCl and extracted into ethyl acetate. The material was dried (MgSO₄), filtered, and concentrated. Crude product was purified on silica gel (500g) by eluting with 75:25 hexanes:EtOAc to afford 620mg (13%) of the title compound as a brown oil. ¹H-NMR (CDCl₃) δ 1.23 (t, 3H), 1.84 (d, 3H), 4.20 (q, 2H), 4.55 (d, 2H), 5.14 (q, 1H), 6.57 (d, 1H), 7.30 (m, 3H), 7.77 (s, 1H); MS [ES] 272 (M+H).

Step C

2-[5-(3-Hydroxy-propyl)-indol-1-yl]-propionic acid ethyl ester



15

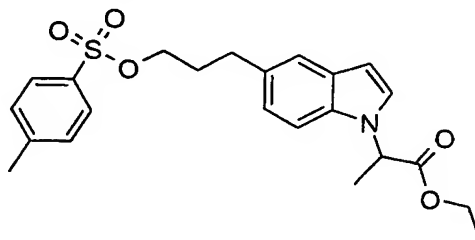
Palladium on carbon (10%, Pd/C) (50mg) was added to a solution of 2-[5-(3-hydroxy-prop-1-ynyl)-indol-1-yl]-propionic acid ethyl ester (1.16g, 4.26mmol) in EtOH (30mL) and the mixture was stirred at room temperature overnight under a balloon of H₂. The mixture was filtered and concentrated to afford 940mg (80%) of the title compound as a brown oil. ¹H-NMR (CDCl₃) δ 1.14 (t, 3H), 1.73 (d, 3H), 1.86 (m, 2H), 2.73 (t, 2H), 3.62 (t, 2H), 4.10 (q, 2H), 5.02 (q, 1H), 6.44 (d, 1H), 6.98 (dd, 1H), 7.16 (d, 1H), 7.37 (d, 1H); MS [ES] 276 (M+H).

20

-386-

Step D

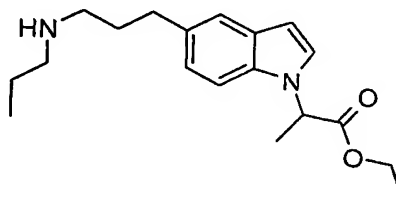
2-[5-[3-(Toluene-4-sulfonyloxy)-propyl]-indol-1-yl]-propionic acid ethyl ester



Standard Procedure (I) which described in Example 261 was utilized with
 5 2-[5-(3-hydroxy-propyl)-indol-1-yl]-propionic acid ethyl ester to afford the title
 compound as a yellow oil. ¹H-NMR (CDCl₃) δ 1.23 (t, 3H), 1.81 (d, 3H), 2.01 (m, 2H),
 2.47 (s, 3H), 2.75 (t, 2H), 4.07 (t, 2H), 4.18 (q, 2H), 5.10 (q, 1H), 6.48 (d, 1H), 6.95 (dd,
 1H), 7.23 (d, 1H), 7.26 (d, 1H), 7.29 (s, 1H), 7.35 (d, 2H), 7.82 (d, 2H); MS [ES] 430
 (M+H).

Step E

2-[5-(3-Propylamino-propyl)-indol-1-yl]-propionic acid ethyl ester



Standard Procedure (J) described in Example 262 was utilized with 2-[5-
 15 [3-(toluene-4-sulfonyloxy)-propyl]-indol-1-yl]-propionic acid ethyl ester to afford the
 title compound as a yellow solid. ¹H-NMR (CDCl₃) δ 0.80 (t, 3H), 1.14 (t, 3H), 1.50 (m,
 2H), 1.72 (d, 3H), 1.87 (m, 2H), 2.56 (t, 2H), 2.65 (m, 4H), 3.10 (br s, 1H), 4.08 (q, 2H),
 5.02 (q, 1H), 6.41 (d, 1H), 6.94 (dd, 1H), 7.18 (d, 1H), 7.32 (d, 1H), 7.67 (d, 1H); MS
 [ES] 317 (M+H).

Step F

2-(5-[3-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl]-
 20 indol-1-yl)-propionic acid

Standard Procedure (A) which described in Example 253 was utilized with
 2-[5-(3-propylamino-propyl)-indol-1-yl]-propionic acid ethyl ester and 5-fluoro-3-methyl-

-387-

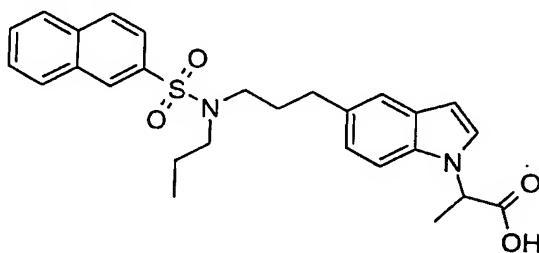
benzo[b]thiophene-2-sulfonyl chloride to prepare the title compound. $^1\text{H-NMR}$; MS [ES] 517 (M+H), 515 (M-H).

The following Examples 414 to 417 were prepared according to the procedure described above in Example 413.

5

Example 414

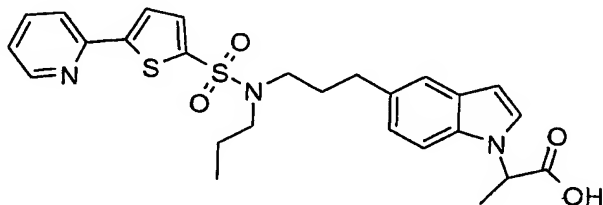
2-(5-{3-[(Naphthalene-2-sulfonyl)-propyl-amino]-propyl}-indol-1-yl)-propionic acid



10 $^1\text{H-NMR}$; MS [ES] 479 (M+H), 477 (M-H).

Example 415

2-(5-{3-[Propyl-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-propyl}-indol-1-yl)-propionic acid



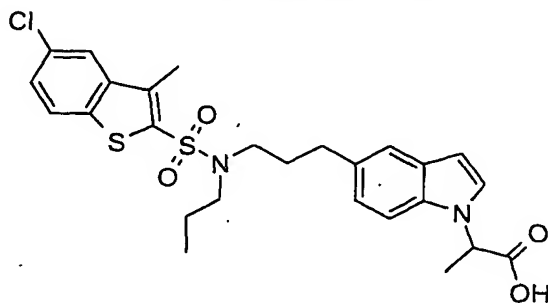
5

$^1\text{H-NMR}$; MS [ES] 512 (M+H), 510 (M-H).

-388-

Example 416

2-(5-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-indol-1-yl)-propionic acid



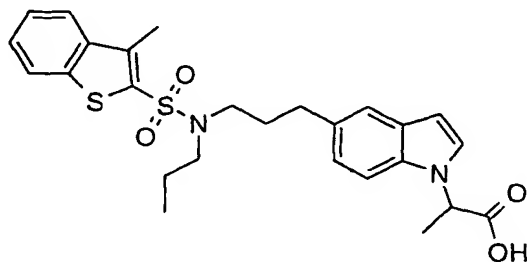
5

¹H-NMR: MS [ES] 533 (M+H), 531 (M-H).

Example 417

2-(5-{3-[(3-Methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-indol-1-yl)-propionic acid

10



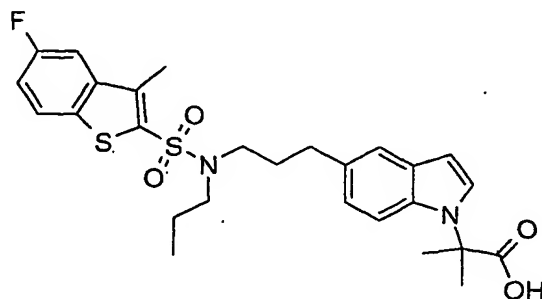
¹H-NMR: MS [ES] 499 (M+H), 497 (M-H).

15

-389-

Example 418

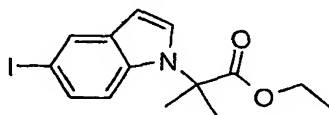
2-(5-{3-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-indol-1-yl)-2-methyl-propionic acid



5

Step A

2-(5-Iodo-indol-1-yl)-2-methyl-propionic acid ethyl ester

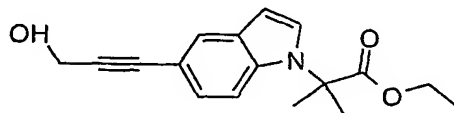


The title compound was prepared by following the procedure described in Example 390, Step A by utilizing 2-(5-iodo-indol-1-yl)-propionic acid ethyl ester to afford the compound as a yellow oil. ¹H-NMR (CDCl₃) δ 1.14 (t, 3H), 1.90 (s, 6H), 4.18 (q, 2H), 6.47 (d, 1H), 6.99 (d, 1H), 7.28 (d, 1H), 7.41 (dd, 1H), 7.99 (d, 1H); MS [ES] 358 (M+H).

10

Step B

2-[5-(3-Hydroxy-prop-1-ynyl)-indol-1-yl]-2-methyl-propionic acid ethyl ester



15

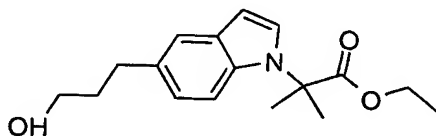
The title compound was prepared by following the procedure described in Example 395, Step B by using 2-(5-iodo-indol-1-yl)-2-methyl-propionic acid ethyl ester to afford the title compound as a brown solid. ¹H-NMR (CDCl₃) δ 1.01 (t, 3H), 1.82 (s, 6H), 4.08 (q, 2H), 4.46 (d, 2H), 6.44 (d, 1H), 7.04 (d, 1H), 7.15 (dd, 1H), 7.24 (d, 1H), 7.67 (s, 1H); MS [ES] 286 (M+H).

20

-390-

Step C

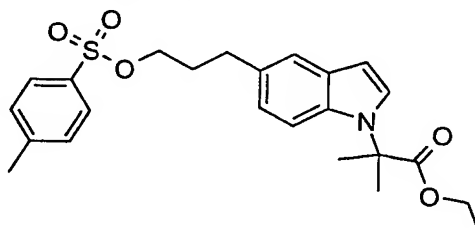
2-[5-(3-Hydroxy-propyl)-indol-1-yl]-2-methyl-propionic acid ethyl ester



The title compound was prepared by using 2-[5-(3-hydroxy-prop-1-ynyl)-indol-1-yl]-2-methyl-propionic acid ethyl ester to afford the title compound as a brown oil. ¹H-NMR (CDCl₃) δ 1.14 (t, 3H), 1.90 (s, 6H), 1.96 (m, 2H), 2.82 (t, 2H), 3.72 (t, 2H), 4.18 (q, 2H), 6.48 (d, 1H), 7.01 (dd, 1H), 7.13 (d, 1H), 7.29 (d, 1H), 7.46 d, 1H); MS [ES] 290 (M+H).

Step D

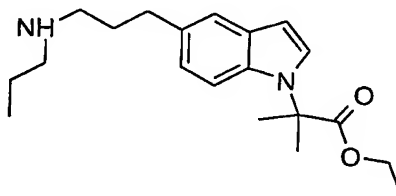
2-Methyl-2-{5-[3-(toluene-4-sulfonyloxy)-propyl]-indol-1-yl}-propionic acid ethyl ester



Standard Procedure (I) which described in Example 261 was utilized with 2-[5-(3-hydroxy-propyl)-indol-1-yl]-2-methyl-propionic acid ethyl ester to afford the title compound as a brown oil. MS [ES] 444 (M+H).

Step E

2-Methyl-2-[5-(3-propylamino-propyl)-indol-1-yl]-propionic acid ethyl ester



Standard Procedure (J) described in Example 262 was utilized with 2-methyl-2-{5-[3-(toluene-4-sulfonyloxy)-propyl]-indol-1-yl}-propionic acid ethyl ester to afford the title compound as a brown oil. MS [ES] 331 (M+H).

-391-

Step F

2-(5-{3-[(5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-indol-1-yl)-2-methyl-propionic acid

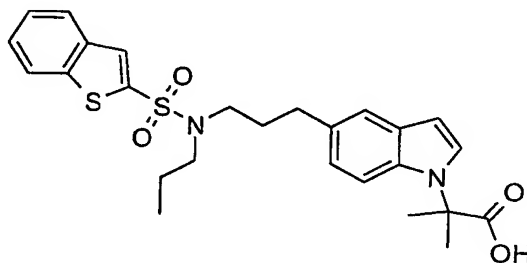
Standard Procedure (A) which described in Example 253 was utilized with
5 2-methyl-2-[5-(3-propylamino-propyl)-indol-1-yl]-propionic acid ethyl ester and 5-fluoro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride to prepare the title compound.
¹H-NMR; MS [ES] 531 (M+H), 529 (M-H).

The following Examples 419 and 420 were prepared according to the
procedure described above in Example 418.

10

Example 419

2-(5-{3-[(Benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-indol-1-yl)-2-methyl-propionic acid



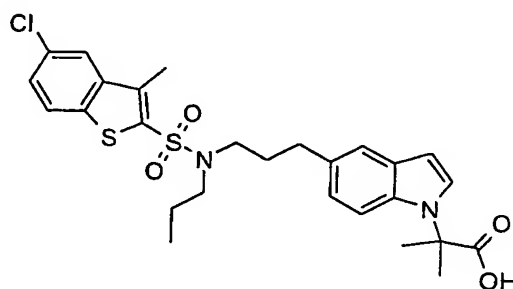
15

¹H-NMR; MS [ES] 499 (M+H), 497 (M-H).

Example 420

2-(5-{3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-propyl-amino]-propyl}-indol-1-yl)-2-methyl-propionic acid

20



¹H-NMR: MS [ES] 547 (M+H), 545 (M-H).